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NERVE GRAFTING AND NERVE SUTURE IN POSTOPERATIVE FACIAL PALSIES

A BRIEF REPORT OF 69 CASES

By KARSTEN KETTEL

Modern treatment of postoperative facial palsies and palsies due to other injuries comprises the following three procedures: decompression of the nerve in the Fallopian canal, nerve suture, and nerve grafting. The symmetry and synchronism of the emotional movements of the face is dependent on the close co-operation of the cortical facial centres of both hemispheres, and the only way to re-establish this cortical interplay in cases of peripheral facial palsy is to repair the injured nerve at the site of the lesion.

Ney in 1922 published a method of intratemporal repair as worked out on the cadaver. Bunnellin 1925 was the first to perform a successful intratemporal suture of the nerve, (published 1927), followed by Martin (1931).

Chief credit for the enormous advances in this field is due to Ballance & Duel (1932) and numerous reports of successful operations from all over the world are now available, especially by Cawthorne, Collier, Findlay, Kettel, Lathrop, Martin, Maxwell, Sullivan and Tickle.

Since 1939, 260 patients have been referred to me, in whom a Ballance-Duel or Bunnell operation was indicated and among these 69 were due to a surgical lesion of the facial nerve of such a grade that a nerve graft or nerve suture was needed.

Of these 69 patients one has been operated on recently, and one has been lost to follow-up. The remaining 67 cases have all been examined by the author.

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INDICATIONS FOR OPERATION

If the palsy occurs after an *interval of freedom* the continuity of the nerve is undisturbed, and the prognosis is good.

If, however, a complete facial palsy arises *in direct conjunction* with the operation, the site of the damage should be explored without delay. The continuity of the nerve is not necessarily broken, and the palsies may in otological surgery be due to a mere pressure on a denuded nerve, a spicule of bone pressed into the sheath, tearing of the sheath or a haematoma. A severance of the continuity should however be strongly suspected and only by exploration can the nature of the lesion be told. The majority of the palsies have arisen in connection with a simple or radical mastoidectomy, or a labyrinthectomy. With the aid of modern antibiotics infection in the cavity is no contraindication to immediate nerve grafting or nerve suture. By immediate operation it is much easier to find the nerve stumps than months or years later, when they must be isolated in granulations and scar tissue. Moreover the muscles have had no time to degenerate, and finally the mind of patient and surgeon can be put at rest.

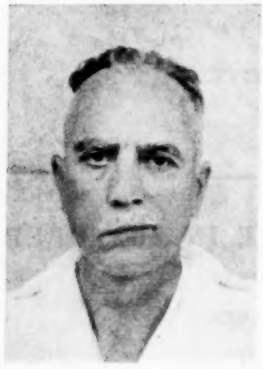
How long after the injury of the facial nerve has occurred can a direct repair be tried?

a) If the site of injury is surgically accessible, which in practice means distal to the geniculate ganglion, and if no degeneration of the muscles has taken place, indicated by a strong response to the galvanic current, the repair is justified at any time.

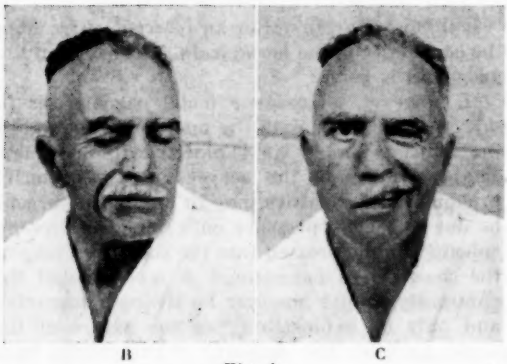
b) If the site of lesion is inaccessible but the muscles have not degenerated an anastomosis be-

tween the facial nerve and one of the other cranial nerves, hypoglossus, glossopharyngeus and especially the spinal accessory nerve (Love & Cannon) should be tried. The result may be a face, which looks normal when at rest, and voluntary movements can be performed but mimicry will never return. (Fig. 1).

c) If the muscles have degenerated any attempt to repair the facial nerve is contraindicated, and plastic operations should be resorted to.



A.



B C

Fig. 1.

In this case an anastomosis between the facial and the spinal accessory nerve was performed on the right side 6 years ago. A: face at rest. B: voluntary movements when he was told to close the eye and draw the corner of the mouth upwards. C: when asked to smile or laugh the movements at the right side were completely lacking. This illustrates, that whenever possible the facial nerve should be repaired at the site of lesion. »Mimique« will never return after an anastomosis operation.

TECHNIQUE

A. Nerve grafts.

The prognosis varies according to the site of the nerve graft (fig. 2) best results being obtained in the first two of the following groups:

1) intratemporal grafts: the whole graft is situated in the Fallopian canal between the geniculate ganglion and the stylomastoid foramen.

2) intra + extratemporal grafts: the proximal end is situated in the Fallopian canal, the distal end connected with the facial nerve stump in the soft tissues.

3) extratemporal grafts: the whole graft is situated outside the stylomastoid foramen.

A perfect coaptation between graft and nerve stumps is all important and should be undertaken under magnification. Some authors use a degenerated nerve graft, maintaining that it is easier to coapt. (Sullivan). In my cases a fresh graft, taken from the ilio-inguinal nerve (Bergström), has been used; this is easy to find and of the right calibre.

B. Nerve suture.

In very few cases it may be possible to perform a direct suture of the facial nerve stumps; in the majority of cases this is impossible. If, however, the lesion is situated in the middle ear it may, according to the technique of Bunnell, be possible to shorten the course of the nerve by lifting it out of the Fallopian canal, and suture the stumps directly across the promotory (»re-routing« of the nerve).

Nerve grafting should be preferred to nerve suture as it leaves the nerve in its bed with an undisturbed blood supply. If the distal end of the graft must be united to the distal end of the facial nerve in the soft tissues outside the stylomastoid foramen nerve sutures should be placed in the sheath only, not through the nerve, as this will produce intraneural scar formation which is a hindrance to the downgrowth of neurofibrils. It is better completely to avoid suture and glue the ends together with plasma according to Sullivan's technique.

The after-treatment is of the greatest importance. The muscles must be kept alive by means of massage and galvanism, for which purpose Clemmesen's myotensor is the machine of choice, because the impulses can be varied according to the chronaxie of the muscles at any given moment. To counteract an overstretching of the muscles a cigarette-holder worn in the angle of the mouth during the day, and a hook from the corner of the mouth round the ear during the night, are valuable; as soon as reinnervation starts, active movements before a mirror should be instituted.

RESULTS

It must be borne in mind that not even the most successful operation will be able to restore function completely. The results, however, may be extremely satisfactory, and they ought to be judged not by how much function falls short of 100 %, but by what has been achieved compared with the condition that would have been present without surgical intervention.

The results may be divided into two groups, according to the condition of the muscles at the time of repair and to the proceeding of the operation.

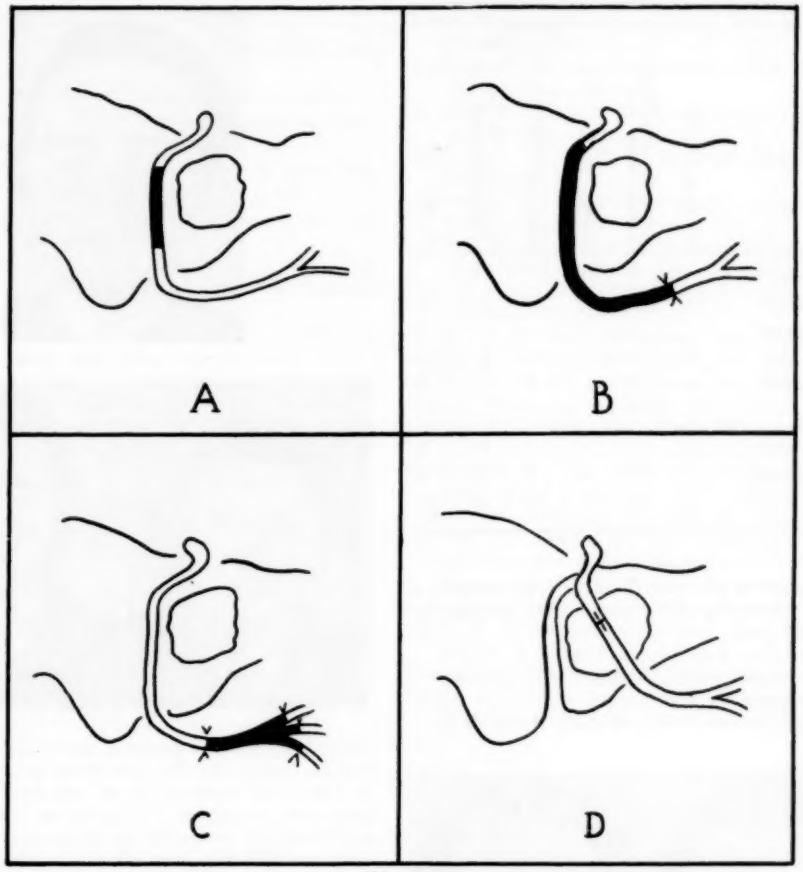


Fig. 2.
A: intratemporal nerve grafting according to Ballance-Duel.
B: intra + extratemporal nerve grafting according to Ballance-Duel.
C: extratemporal nerve grafting according to Ballance-Duel.
D: nerve suture after "re-routing" of the nerve according to Bunnell.

A. Cases, in which no degeneration of the muscles had taken place and in which the operation was successfully performed.

Only when these conditions are fulfilled, good results can be expected. To this group 53 cases belong. (Fig. 3).

A clinically satisfactory result was obtained in 48 cases or ca. 90 % (Figs. 4 and 5), insufficient re-innervation was noted in 4 cases, (ca. 8 %), while in 1 patient no re-innervation at all took place. (ca. 2 %).

I am nuable to explain, why in one case (a woman 72 years of age) no re-innervation took place, and why the result in 3 was unsatisfactory. Perhaps the coaptation was bad, as these operations were done before I started using magnification. In the last case a sarcoma was removed from the descending part of the facial nerve, and the patient was treated by X-rays postoperatively, which may have damaged the graft and neurofibrils. She is, however, steadily improving.

B. Cases, in which the muscles had degenerated partially at the time of repair or insurmountable technical difficulties were encountered.

To this group 14 patients belong. All the patients had of course been told in advance that in their cases the operation had to be regarded as an experiment and that the final issue could not be foretold.

In 6 cases (all nerve graftings) no-re-innervation took place, in 8 (1 grafting, 7 sutures) it was clinically unsatisfactory.

The technical difficulties, to me insurmountable, applied especially to extratemporal repairs, where the palsy was due to removal of a retromandibular tumor, a tumor of the parotid gland or to a gunshot lesion. In these cases the bed consisted of scar tissue, where only minor strands of the distal end of the facial nerve could be found. If a minor strand, connecting the proximal and distal ends of the facial nerve at the site of injury is found, it should be resected and substi-

	No re-innervation	Clinically unsatisfactory re-innervation	Clinically satisfactory results: smile	smile and close eye	smile, close eye and wrinkle forehead	In all
Nerve grafting.						
1) intratemporal ..	1	3	4	18	5	31
2) intra + extra temporal	0	1	2	10	1	14
3) extratemporal ..	0	0	0	0	0	0
Nerve suture.						
1) intratemporal ..	0	0	1	7	0	8
2) extratemporal ..	0	0	0	0	0	0
In all	1	4	7	35	6	53

Fig. 3

A total number of 53 cases. in which the conditions for and the proceeding of the repair were satisfactory, were operated on.
No re-innervation: 1 case or ca. 2 %.
Insufficient re-innervation (clinically unsatisfactory result) = 4 cases or ca. 8 %.
Clinically satisfactory result: 48 cases or ca. 90 %.

Fig. 4.
Intratemporal nerve grafting 8 mm, right side. Pictures taken 1¾ years after the operation. Steadily improving. The minimum requirement for the results to be classified as good is that the paresis must not be noticed when the face is at rest and that the patient can smile and laugh to a certain degree. Among 53 patients, in which no degeneration of the muscles had taken place and in which the operation was successfully performed 7 recovered as illustrated above.

tuted by an end-to-end graft. Attempts to preserve this and add a end-to-side graft nearly always fail.

The interval between damage and repair has varied widely; 8 nerve graftings or sutures have been performed, almost immediately, 8 within a week, 6 within two weeks, 17 between one and

Fig. 5.
Intratemporal nerve grafting, right side 10 mm. Before and 2¾ years after the operation. Among 53 patients, in which no degeneration of the muscles had taken place and in which the operation was successfully performed, 35 recovered as illustrated above, 6 even better as they also were able to wrinkle the forehead.

12 months, the rest over a year after the nerve had been injured.

The length of the graft has varied from 4 mm to 50 mm, and some of my best results have been obtained in cases where a long graft (35—50 mm) has been used.

With one exception the movements always started in the muscles at the mouth, being for months preceded by a feeling of returning tonus.

The time when the first signs of returning mobility were noted, has varied from 4—24 months, on the average being 10 months.

Modern antibiotics have almost made simple mastoidectomies superfluous, and thus a major source of postoperative palsies has been eliminated. However radical mastoidectomies are indicated in a great number of cases. To the list of sources may now be added fenestrations, and even if today a better technique is prevailing, damage to the facial nerve can hardly be completely avoided. Also palsies due to non-surgical accidents of varying nature may require a repair. If this is undertaken at once by a surgeon especially trained for this purpose, the patients have a good chance of obtaining a clinically satisfactory result.

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ISCHAEMIC FACIAL PALSY

RESULTS OF DECOMPRESSION OF THE FACIAL NERVE ACCORDING TO BALLANCE & DUEL IN 108 CASES

By KARSTEN KETTEL

The term Bell's palsy has been used indiscriminately for almost every kind of peripheral facial palsy, regardless of its nature. In this paper the term is restricted to cases in which the facial palsy is the only clinical symptom, and in which it has been impossible to demonstrate a local causation.

PATHOLOGY

The primary cause of the majority of Bell's palsies is an ischaemia of the facial nerve near the stylomastoid foramen (Audibert et al., Cawthorne, Sullivan, Kettel) probably caused by arteriolospasm (Hilger). As a result of this, various structural alterations take place in the facial nerve between the lateral semicircular canal and the stylomastoid foramen, and in some cases also in the surrounding bone. The extent of these alterations depends upon the severity of the interruption of blood supply, which may be short and transient or prolonged. The nerve becomes unduly constricted at the stylomastoid foramen and oedematous proximal to this point, while tiny haemorrhagic streaks are seen running longitudinally within the sheath (Cawthorne). As a further result of the ischaemia there may in severe cases be exudation into the mastoid cells and especially around the stylomastoid foramen, together with bony necrosis in the walls of the cells and in the Fallopian canal (Kettel, confirmed by Skoog, Hall, and Flodgren). This necrosis is both micro- and macroscopically of purely degenerative type, and never inflammatory.

The swelling of the nerve within the Fallopian canal results in a secondary compression of the adjacent blood and lymph vessels, and consequently a vicious circle arises.

The nerve looses its conductive power on account of ischaemia, not because it becomes com-

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pressed within the facial canal. This has been proved experimentally (Lewis, Pickering & Rothschild, Denny-Brown & Brenner, Grundfest) as well as clinically (Kettel).

It seems that the cause of the palsy and the pathological alterations are both connected with the environment, occurring more often and more severely in the northern countries (Martin).

But whereas the pathogenesis seems clear, our knowledge of the etiology is extremely limited. It should only be mentioned that many patients had been exposed to cold immedately before the palsy arose, but other factors such as allergy and emotional strain may cause an ischaemic facial palsy.

THERAPY AND PROGNOSIS

Knowing practically nothing about its etiology we cannot prevent Bell's palsy from arising, but can only try to combate the primary cause, the ischaemia and prevent or at least reduce the secondary compression of the vessels within the facial canal.

Medical treatment is the therapy of choice as it aims at correcting the primary disturbance of the vasa nervorum and has resulted in the complete recovery of 75—85 per cent of cases. For this purpose drugs with vaso-dilator effect have been used, such as nicotinic acid, intravenous histamine, and papaverine (Hilger; Loomis; Ingelstedt & Thees; Skinner). Sympatholytic drugs have also been tried, such as ergotamine tartrate and tetraethylammonium chloride, as well as cervical sympathetic block, lately cortisone has been used with good results. (Rothendler, Thomsen).

Surgical intervention is nonetheless indicated in a limited number of cases. On the present indications surgery can only aim at correcting the sequels: oedema, compression of the vessels within the facial canal and possibly angulation of the nerve at the point of vasoconstriction.

The great problem, however, is to find a sound basis for operation. In selecting cases for operation many authors (Tickle, Cawthorne, Sullivan) rely completely upon the response to Faradic current, claiming that a complete recovery will never take place when the response is negative. Others however (Kettel, Martin, Violé, Rasmussen, Mayer) do not consider this a reliable indicator, having seen many patients with a negative response recover spontaneously. In exactly the same way opinions differ regarding the value of electro-myography (Sullivan, Collier).

Personally I have on empiric indications operated on 108 cases of ischaemic facial palsy. This group consisted of 74 women and 34 men, and 60 of them were between 20 and 39 years of age. With very few exceptions I have been able to re-examine personally all the cases; the remaining few were examined by their own doctors.

Decompression was performed on the following 3 indications.

a) Delay in recovery.

The majority of the cases showed no signs of recovery after two months of observation. The time limit is based upon the fact that upon re-examination of 169 cases of otitic palsy, which were conservatively treated as regards the nerve, a complete recovery was never seen when the first signs of spontaneous movement began later than the second month. A report by James & Russell shows that this also applied to the ischaemic palsies conservatively treated they examined.

The group operated on this indication comprises 26 women and 18 men. They all had a complete palsy, with negative Faradic response and in the majority of cases decompression was performed 2—4 months after onset. In 39 of the 44 cases treatment, and all has been completed of these have been re-examined. The results are as follows:

In 35 the palsy could not be detected when the face was at rest.

In 3 the palpebral fissure was a little diminished on the side affected.

In 1 there was a very slight contracture.

33 patients could move the forehead to varying degrees.

All the patients could close and screw up their eyes.

12 could smile to the degree shown in Fig. 1 B.

21 could smile to the degree shown in Fig. 1 C.

6 had recovered completely as shown in Fig. 1 D.

In all cases synkineses varying from extremely slight to rather pronounced were noted.

It is impossible to tell what the result would have been without decompression. The criticism has often been raised that the surgeon has taken credit unjustifiably for improvements following decompression, and there is no doubt that many of these patients would have recovered at least partially without the operation. Two facts have however convinced me that in cases of delayed recovery operation has hastened and improved the final result. Firstly, like others I have in many cases observed movements to start immediately following operation. This is probably due to relief of the secondary compression within the facial canal of undamaged axons and their vessels. Secondly, among the patients of James & Russell, suffering from ischaemic facial palsy and referred because of delay in recovery, 17 had had a palsy of more than two month's duration, and none of these recovered completely. »In 10 cases there was obvious contracture of the previously paralysed side, and in 3 cases this was severe.« Thirty of my patients in this group came to operation two months or more after the onset, and of them 6 recovered completely (Fig. 1 D),

A B C D

Fig. 1.
Different degrees of mobility of the mouth regained. All the patients had a palsy on the right side. A, slight. B, more pronounced. C, strong. D, full mobility. All the patients could close and screw the eye tightly up.

15 to the degree illustrated in Fig. 1 C, and 9 as in Fig. 1 B. In only a single case a slight contracture was noted. It appears therefore that decompression counteracts the development of contracture, and moreover can make a manifest contracture disappear, as will be seen later.

Consequently, comparison between the results obtained in palsies showing delayed recovery by medical (James & Russell) and by surgical (Kettel) treatment, shows that surgery gives better results, but also that complete recovery is the exception, certainly not the rule. Contractures are almost avoided, and the synkineses seem to be less pronounced than in cases treated medically (Cawthorne).

Could still better results have been obtained by prompt decompression, by which is to be understood an emergency operation?

Bunnell has recently made the following statement: »The only possible time for prophylaxis or prevention of Bell's palsy is during the first few hours — three hours if the blockage of circulation is complete, but a few more if partial. Prompt decompression will keep the nerve alive. If decompression is not done then, the ischaemia will result in a degree of damage to the nerve ranging from temporary palsy to permanent paralysis.«

But any operation as a routine method at the onset of palsy is of course out of the question, since 75—85 per cent of all ischaemic facial palsies recover under medical treatment, and we have at present no means of recognising the 15—25 per cent of more serious cases, either by clinical examination or tests. Regarding the fresh palsies Martin says that »since no criteria for immediate operation are agreed upon, more nerves will be saved by medical therapy than by perhaps unnecessary surgery«. I quite agree with Martin, and moreover I should like to add that even if we did know in which cases medical treatment would fail, some operation which could deal with the underlying cause, the primary vasoconstriction, would be the method of choice rather than decompression. As long as an ideal procedure is not available for this purpose, we would have to content ourselves with decompression in these 15—25 per cent of more serious cases, while fully realising that by decompression we deal only with the secondary compression of the facial nerve, and not with the real cause of the palsy.

Consequently, when confronted by a patient with fresh palsy, we do not today know when or exactly how to operate. We only know that in cases where no signs of returning mobility have appeared after two months of observation, a complete recovery is highly improbable, and that decompression in these cases has proved its value. Until better tests are available, I shall continue to observe my patients for two months before comtemplating a decompression.

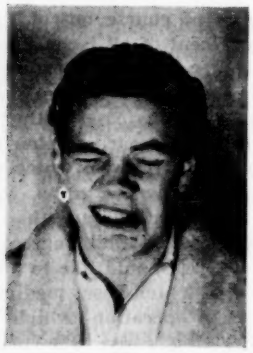
b) Cessation of the spontaneous recovery of mobility before complete restitution is obtained.

While it is impossible to tell with certainty how much a patient with a complete palsy has gained by decompression, it is easy to evaluate the effect of the operation in cases where the spontaneous return of movement has stopped short of complete recovery. A resumption of improvement has never been observed when spontaneous recovery has once ceased at a certain stage.

The effect of decompression on cases in this group is illustrated by the following example:

A man 17 years of age had developed an ischaemic palsy of the left side, becoming complete in 6 hours, 7 months before admission. He gradually improved under conservative treatment, but the improvement stopped after 5 months. (Fig. 2 A). Apart from the palsy nothing abnormal was found by the very thorough examination. Two months after the improvement had stopped, or 7 months after the onset, a decompression was done. The mastoid cells were extremely haemorrhagic, and the bone around the mastoid foramen soft. The facial canal was normal, but the nerve

oedematous. The immediate improvement is clearly illustrated by the pictures. The first photograph (Fig. 2 A) was taken before, and the two others six hours after the operation.



A

B C

Fig. 2.

Peripheral facial palsy, left side.
A: Maximal degree of mobility before the operation. B and C: six hours after decompression on the left side.

The same prompt results have been obtained in several other cases. M o r r i s performed a successful decompression on one of his patients 8 years after the onset, and can be added a further case of partial recovery on whom I performed decompression 14 years after the palsy started. »Mimique« improved immediately after the operation. This may seem incredible, but is nonetheless a fact.

My patients falling into this group number 30 women and 11 men. Two died years later from unrelated causes. The remaining 39 have all been re-examined:

Considerable improvement followed in 19 cases. Two of these, who were decompressed 1 and 3 months after the cessation of spontaneous improvement, recovered completely.

In 11 cases a moderate improvement resulted, which was however valued by all the patients.

In 3 cases the improvement was only slight.

In 2 cases the result is doubtful.

In 3 cases there was no improvement, but one of these was relieved of a troublesome headache and a feeling of stiffness in the cheek.

In 1 case the patient was worse than before operation.

From this it can clearly be seen that decompression may give valuable results even when the operation is done years after spontaneous improvement has stopped. Further, many patients are either completely freed of annoying stiffness of the cheek, or have this symptom significantly lessened. Finally contracture disappeared in several cases after decompression. (K e t t e l).

I must, however, give a strong warning against performing the operation on insufficient indications, as it is impossible to tell beforehand whether improvement will result. The outcome depends upon whether the remaining palsy is due to permanent degeneration of the nerve on which decompression can have no effect, or is due to pressure upon the vessels in the facial canal which may be relieved by operation. The one case should also be remembered in which a patient got worse in spite of an operation which appeared perfect to the maked eye.

If the power of movement is very bad, if the galvanic response, due to adequate treatment by galvanization and massage, is strongly positive, and if on decompression an atrophich nerve is found, the best course is to resect this part of the nerve and insert a graft.

c) Relapsing palsies.

There has hitherto been unanimous agreement between C a w t h o r n e, S u l l i v a n and myself that decompression prevents a recurrence of the palsy. In 14 years I have operated on 23 patients with relapsing palsies, but only recently have I seen two patients, by chance both at the same time, who suffered from a recurrence on the side previously decompressed. These relapses occurred 11 years and 1 year after their respective operations. In both, however, the palsy disappeared again spontaneously and completely in a short time.

This is clinically a very distressing phenomenon, but most interesting from a pathological point of view. It confirms that the primary cause of palsy is ischaemia of the nerve, not the secondary compression, as the canal in which the compression takes place had been opened previously, and also suggests that not in all cases does the decompression lead to the setting up of a collateral blood supply. I had previously assumed that this always occurred.

The group comprises 23 patients, 18 women and 5 men, who had had attacks of palsy from 2 to 9 times.

23 patients, all with complete palsies, were operated on shortly after the recurrence, and the results are as follows:

4 patients recovered fully after decompression.

14 patients recovered with only minor defects.

Having spontaneously recovered only partially after their first attack, 5 patients regained movement to the same extent after decompression. In

1 case a relapse occurred 11 years later with ensuing recovery to the same extent as before.

I have previously always maintained that decompression was absolutely indicated as soon as a recurrence took place, and that it would prevent a further relapse. But observation of the two recurrences in spite of previous decompression has made me alter this indication, and I now treat patients with a relapse in the same way as cases of fresh palsy. They are observed for two months under careful conservative treatment, and a decompression is performed at the end of this time if no sign of returning movement can be noted.

SUMMARY

The majority of cases of Bell's palsy are due to ischaemia of the facial nerve near the stylomastoid foramen. Following lack of blood supply the nerve loses its power of conduction, and venous stasis arises with ensuing swelling of the nerve, which becomes secondarily compressed within the Fallopian canal.

The therapy of choice is medical treatment aiming to relieve the vasoconstriction and maintain the contractility of the muscles. Surgical decompression of the facial nerve is indicated in a limited number of cases, and the results of 108 operations are briefly recorded.

Decompression should be performed in both fresh and relapsing palsies if no signs of spontaneous movement are observed after two months of observation. With patients in whom spontaneous recovery has ceased before complete restitution has been obtained, further improvement may be expected from decompression.

A detailed report will appear in the Archives of Otolaryngology.

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TUBERCULOUS AND TUBERCULOID COMPLICATIONS DURING TREATMENT OF LUPUS VULGARIS WITH CALCIFEROL

By POUL V. MARCUSSEN

From 1943 to 1952 calciferol (vitamin D_2) was the drug of choice for treating lupus vulgaris and verrucous cutaneous tuberculosis (3, 6), and it is still rather extensively used. The effect is very definite (33), but is limited by intolerance, so that freedom from clinical and histological signs is obtained in no more than 85 per cent of cases (23), if the treatment is not supplemented by local treatment. The incidence of relapse is high. Of a series of patients observed for 3 years after the conclusion of the treatment only 30 per cent were free from recurrence (23). It is strange that the effect of calciferol on other forms of cutaneous tuberculosis is uncertain (32), and even unfavourable on scrofuloderma (28) and particularly on erythema induratum. Vachon (39) as early as in 1944 observed tuberculide, glandular swelling,

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and iridocyclitis during treatment of erythema induratum with calciferol. Later there have been seen local ulcerative degeneration, severe general symptoms, activation of pulmonary tuberculosis with haemoptysis and death (5, 28, 32). Such complications to calciferol treatment are only to a small extent observed during the treatment of lupus vulgaris and verrucous cutaneous tuberculosis. The literature nevertheless contains no small number of reports on complications: papulonecrotic tuberculides (1, 12, 19, 25—27, 31, 37), lichenoid tuberculides (5, 12, 19, 25, 27), annular, sarcoid-like tuberculides (12, 44), and atypical tuberculides (11, 20, 22, 44). Supposed activation of pulmonary tuberculosis has been observed (9, 18, 21, 27, 30, 37, 45), in most cases consisting of development of cavities in infiltrative processes. Occurrence of tuberculous processes in the lungs has been described by Dowling, Gauvain, and Macrae (5) and Sturm (37). Of tuberculous processes in other organs the following have been observed: peripheral adenitis (1), intrathoracic adenitis (10), mastoiditis (37), bone focus and epididymitis (12), spondylarthritis (45), and meningitis (12, 37). As the various series of cases reported differ considerably with regard to average age, extent of treatment, as well as period and mode of observation it is difficult to judge the frequencies of these complications.

Of Grzybowski and Miedzinski's 350 patients, including 246 with lupus vulgaris, 24 had complications. Though these phenomena have occurred within the period of treatment, which is 1 or 2 years at least, we are hardly justified, without further analysis, in postulating a relationship to therapy, because patients with lupus vulgaris have an active tuberculous infection. This previously often was complicated by pulmonary or extrapulmonary tuberculosis, but of its untreated course our knowledge is deficient. Kalkoff's (14) review of the early literature shows the mortality of pulmonary tuberculosis among lupus patients to have been 22—28 per cent, while the total mortality of tuberculosis in this group was 30—45 per cent. Kalkoff found that the mortality of pulmonary tuberculosis among lupus patients is six- or seven-fold higher than the general mortality of pulmonary tuberculosis in patients without skin lesions, the highest among men in the age-class of 30 to 35 years. Lupus was in the beginning of the century often complicated by pulmonary and extrapulmonary tuberculosis, but this seems to have changed. In the series of patients from the Finsen Institute just prior to the institution of calciferol treatment (average age 60) only three instances of tuberculosis, two of which were renal, were found among the 29 cases of death, where the cause of death was verified. An analysis of the incidence of tuberculous organ complications in patients with lupus vulgaris under the present economic and social conditions does not seem available. The difficulty of assessing the complications appears from Sonne's (31) thorough examinations of six cases where exacerbation of an existing pulmonary tuberculosis occurred among 13 patients with pulmonary changes. One patient experienced exacerbation twice following calciferol treatment, but in the remaining patients no definite conclusions could be drawn as to the cause.

The *object* of the present investigation has been to record all tuberculous and tuberculoid complications to calciferol treatment and study their relation to the average age, tuberculin reaction, dose of calciferol, and result of treatment.

The *total series* examined comprised 284 patients treated with calciferol in one to three courses. Regarding technique and observation reference is made to Sonne's (31) work from 1950 and to a previous publication by the author (23). A large proportion of the patients were included in Sonne's series. However, with a view to prolonged observation the patients who could not be expected to appear for control (especially foreigners and patients with severe, non-tuberculous diseases) have been ruled out and the series has been provided with serial numbers. Since 1950 the patients have on each admission been examined for tubercle bacilli by culture from sputum, gastric lavage water, sterile urine, and biopsy specimens. During the whole period the patients were submitted to systematic X-ray examinations of the lungs and suspicious regions, as well as to E. S. R. determinations, quantitative tuberculin test, weight measurements, and at intervals temperature measurements. All the patients, apart from 27, who died during the period of treatment and observation, were controlled on the last examination in autumn 1953; ten were lost to observation 500 to 1200 days after the conclusion of treatment. 21 of the patients were in part under observation in a tuberculosis institution. The average observation period for the surviving patients was very nearly 6 years, reckoned from the commencement of treatment, for the last 3 years with complete tuberculosis control. The importance of systematic control appears from the fact that about twothirds of the mild complications were detected within the later half of the 6-year period, while more pronounced complications were ascertained with almost equal frequencies in the two halves. The number of mild complications is therefore probably somewhat smaller than if systematic examinations had been carried through during the whole period.

Results: It appears from Table 1 that among 284 calciferol-treated lupus patients 36 (12.7 per cent) were found to have complications in one or more organs. Six of these had more than one complication (Table 2).

Skin-lesions (tuberculides): Three patients had previously had tuberculides, of whom two had erythema induratum. These two patients ex-

perienced relapse of the erythema induratum. In 17 cases tuberculides developed for the first time (two ulcerative, six papulonecrotic, three lichenoid, four annular, two indurative). Four of these patients had two outbreaks, and three more had outbreaks under repeated treatment. The morphology was the same in the cases of repeated eruptions, except in one, where lichenoid tuberculides were later followed by annular. The first eruption occurred in all patients at a point of time when the lupus was about to subside, but with no relation to the total dose of calciferol, which varied from less than 200 mg to over 1 g. These skin lesions persisted for a fairly long time, one for 23 months and only five for less than 5 months. The general condition was affected but little. The majority complained of tiredness, however. Three had periods with fever and three transitory lung infiltrations, one also had unilateral epididymitis. 17 patients had a raised E. S. R. The tuberculin reaction was of the same strength before and after, but in three instances stronger during the presence of the eruption. The tuberculin reaction before the treatment was generally somewhat smaller than in the total series. Apart from the four cases with erythema induratum, the treatment was resumed or continued with the result that 14 out of 19 patients became free from signs of lupus vulgaris and experienced no relapse during the observation period. Three patients have died of non-tuberculous diseases. None of the remaining patients display signs of active tuberculosis. In one case hilus gland swelling occurred, which has persisted unchanged since. 13 of the patients have been examined systematically for tubercle bacilli. In only one case were tubercle bacilli demonstrated after repeated biopsy from an ulcerative tuberculide.

Pulmonary changes. In addition to simple calcifications, other abnormalities were demonstrated radiographically in 80 of the 284 cases (Table 3) before the treatment. None of these patients showed signs of clinical activity before the commencement of treatment. Two patients experienced aggravation of the condition during the treatment. They died later, but it was impossible to say for certain whether the fatal course was a consequence of the treatment (31). For the purpose of obtaining further clarity two patients were submitted to another two courses of calciferol treatment after exacerbation of the pulmonary afection had been observed during the first course.

Case 1. In a woman, aged 55, cavernous tuberculosis in the rt. apex (human type) had been ascertained 12 years previously. The lung picture had remained stationary for 10 years. Gastric lavage water presented no growth of tubercle bacilli. The patient's lupus subsided after treatment with 720 mg calciferol; but at the same time development of cavities was demonstrated in the rt. apex and fresh infiltration in the lt. After conclusion of the treatment the infiltration in the lt. lung subsided, while the picture of the rt. lung remained unchanged for 21 months. The patient was abacterial. The lupus recurred and calciferol treatment was resumed, but after 300 mg cavities developed again. The patient was still abacterial. The lung picture remained stationary for 23 months, after which treatment of the lupus was resumed. After 900 mg cavities were again seen to develop, and tubercle bacilli were found in gastric lavage water and urine. During the three radiographically demonstrated exacerbations the E. S. R. was raised, and Mantoux' reaction steadily decreasing. The patient was afebrile, and the general condition uninfluenced. After 2 years of observation the lung picture was unchanged, the E. S. R. normal, and the patient abacterial without having received other treatment.

Case 2. A woman, aged 36, had 4 years before the treatment had bacillary tuberculosis in the rt. lung (human type). Annual control showed the lung picture to be stationary, and tubercle bacilli were not demonstrated by gastric lavage. After treatment with 120 mg calciferol for lupus vulgaris the patient lost weight, the E. S. R. rose, and a fresh infiltration in the rt. lung was ascertained, while at the same time the lupus subsided. After a pause of 3 months, during which the infiltration in the lung disappeared, the treatment was resumed and carried through with 990 mg calciferol with no change in the X-ray picture or in the clinical condition. Lupus recurred 6 months later and calciferol was therefore given again, but after no more than 82 mg a fresh infiltration in the rt. lung and a raised E. S. R. were noticed. The treatment was nevertheless carried through, until the patient had received 570 mg calciferol. The lupus had then been completely cured. The lung infiltration disappeared in the course of 2 months despite continued treatment. After renewed recurrence of the lupus 12 months later calciferol treatment was resumed again. Following administration of 195 mg infiltration in the rt. lung and a raised E. S. R. were observed for the third time. The treatment was then discontinued. The lung infiltration disappeared within about 2 months. The patient has since been observed regularly for 18 months. The lung picture is stationary, the E. S. R. normal, and the patient is abacterial.

There can thus be no doubt that calciferol treatment may activate pulmonary tuberculosis, preferably at the point of time when the lupus is about to subside. It has been impossible to assess the change of activation on the basis of the X-ray picture before the treatment. However, all the patients in whom activation occurred had been treated for clinically active pulmonary tuberculosis within the past 15 years. 11 patients with perfectly normal lung pictures before the treatment developed radiographically demonstrable changes in eight cases immediately following cure of the lupus and in four up to 12 months after the patient had become clinically symptom-free but was still under treatment. In three patients several minor infiltrations were seen scattered over the lung fields, and in seven an infiltration outside the hilus (in six of these outlines of hilus glands were later demonstrated). Finally, there was in one case found infiltration in the apex.

In one case tubercle bacilli were traced by

Table 1.

Prev. demonstr. and existing changes (anamnestic, radiographic, and clinical)		Recurred or exacerbated	Fresh eruptions	Total number and percentage of complications	T. b. demonstr.	Number without recurrence of lupus vulgaris at final exam.
Skin	3	2	17	19 (6.7 %)	1	14 out of 19
Lungs	80	4	12	16 (5.6 %)	4	14 out of 16
Other organs	35	0	6	6 (2.1 %)	5	5 out of 6
Peripheral lymph nodes	95	0	2	2 (0.7 %)		1 out of 2
		6	37	43		79.1 per cent

gastric lavage without the lung picture being definitely abnormal. This patient has afterwards been controlled during repeated stays in hospital; but signs of tuberculosis have not been demonstrated since. In ten patients the changes were transitory, of 2 to 24 months' duration. In 11 patients the E. S. R. was raised, in four there was coughing and expectoration, in three tiredness, in two loss of weight, and in one fever. In four cases the pulmonary changes were attended by tuberculide and in one by epididymitis. The sizes of the 24-hour dose and the total dose of calciferol did not differ from those in the remaining series. Four of the patients had received less than 200 mg and four more than 1 g. In two of the 12 patients the treatment was discontinued, while in the remaining it was continued without causing further signs or symptoms. Ten of the patients obtained clinical cure of the lupus and had had no relapse at the conclusion of the investigation, by which time none of the patients presented signs of pulmonary tuberculosis. The pulmonary changes had disappeared, except in one case an infiltration in the apex.

Table 2.
Cases with concurrence of symptoms from two or more organs.

Skin — Lungs	3
Skin — Lungs — Epididymis	1
Lungs — Kidneys	1
Kidneys — Epididymis	1
	6

Table 3.
Changes in the lung pictures of 284 untreated lupus patients with an average age of 60.

	Number	Exacerbated
Apex infiltration alone	42	1
Pleural cast alone	13	
Hilus glands alone	10	
Apex infiltr. with cavities	5	2
Apex infiltr. and pleural cast	5	1
Apex infiltr. and hilus glands	2	
Pleural changes and hilus glands	3	
	80	4

Regional adenitis. 95 out of the 284 patients had had tuberculous affection of cervical glands. In none of these cases was relapse of adenitis seen during the calciferol treatment. Indolent regional adenitis developed in two patients who had not previously had this affection. Biopsy was not made.

Other organs. Four cases of tuberculosis in other organs were discovered during and after the calciferol treatment. One case of joint tuberculosis proved, however, by revision of the past history to have caused symptoms several years before the treatment. In three cases renal tuberculosis was demonstrated, 6, 8, and 12 months respectively after the conclusion of calciferol treatment with cure of the lupus. One of these cases occurred simultaneously with exacerbation of cavernous pulmonary tuberculosis, and another simultaneously with tuberculous epididymitis. One patient developed bilateral renal tuberculosis ending fatally 3 years later. In the three cases a raised E. S. R. was found, and in one attending fever. None of the patients had presented chemical, microscopical or bacteriological changes in the urine during the treatment. In 35 of the 284 patients there was clinical or anamnestic evidence of organ tuberculosis of earlier date: in 19 cases osteitis, in ten arthritis, in three peritoneal or mesenterial gland tuberculosis. The following lesions occurred in one case each: abscess, tenosynovitis, periostitis, renal tuberculosis. Four of these showed signs of activity before the calciferol treatment, and three were submitted to surgical treatment during or immediately after this, as no improvement was observed. A case of bilateral renal tuberculosis, where one kidney had been removed several years previously, became symptom-free during the treatment. The fact that three instances of renal tuberculosis developed immediatey after the conclusion of calciferol treatment is remarkable, but allows of no conclusions.

Mucous membranes. 36 of the 284 patients had previously had lupus of the mucous membranes, but activity during the calciferol treatment was not observed. 43 patients had active lupus of the mucous membranes, which in 39 cases subsided earlier than the lupus of the skin. In four cases ulcerative reaction occurred.

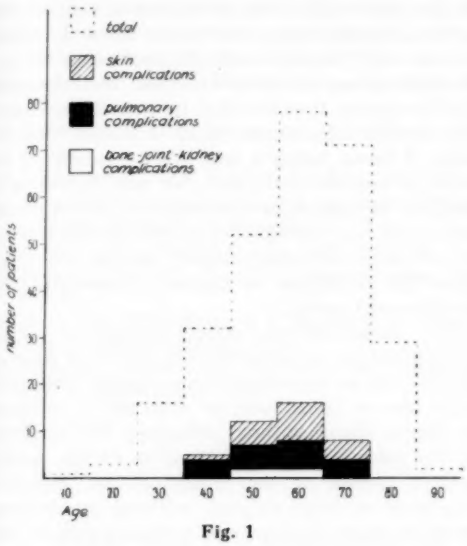

Fig. 1

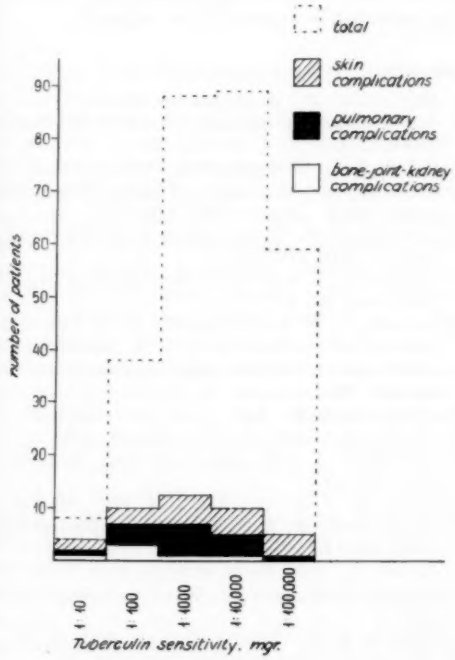

Fig. 2

Age and tuberculin reaction. It appears from Fig. 1 and 2 that the age incidence was the same in the group of complicated cases as in the total series. Skin and lung affections thus occurred in an age-class where they are otherwise rare. In all groups the patients who later had complications showed the least sensitivity to tuberculin. The difference was, however, so small that the tuberculin reaction in the individual case was of no prognostic value.

DISCUSSION

There can hardly be any doubt that exacerbation of pulmonary tuberculosis and relapse of erythema induratum may be consequences of calciferol treatment of lupus vulgaris, whereas the present series of cases does not allow of conclusions as to activation of tuberculous processes in other organs. Tuberculoid lesions in the skin, lungs, and epididymis have been observed in patients who have not previously had such. These chiefly benign lesions occurred single or in combination, and were in some instances accompanied by fever, tiredness, and a raised E. S. R. Some patients later developed bacillary renal tuberculosis, while tubercle bacilli in rare cases only were demonstrable in the skin and gastric lavage water. The changes, apart from the renal and one-third of the pulmonary, occurred at a point of time when the lupus was about to subside, but independently of the total or the 24-hour dose of calciferol. Continuation of calciferol treatment after lupus had subsided generally caused no fresh signs, whereas resumed treatment of persistent lupus or treatment of recurred lupus as a rule brought about relapse of the same cutaneous and pulmonary processes. Freedom from relapse of lupus during the observation period was more frequent in the group of complicated cases than in the total series. The age distribution was the same for patients with and without complications. Thus, tuberculides and lung infiltrations were found chiefly in an age group where these phenomena are otherwise rare. The tuberculin reaction, determined before the treatment, was somewhat weaker in the group of complicated cases.

There is, in other words, reason to suppose that the observed complications were related to subsidence of the lupus under calciferol treatment in patients with a comparatively weak tuberculin reaction. The lack of information on spontaneous occurrence of such complications in an untreated series of cases is therefore presumably of no great importance. As tubercle bacilli have been traced in nearly all cases of severe complications and a few of the mild, there is much evidence to suggest that all the complications were of tuberculous origin. This hypothesis is borne out by the results of the present investigations into the effect of calciferol. Calciferol causes lupus to subside clinically and histologically, but several workers (23, 24, 29, 41) have cultured tubercle bacilli from cicatrices where repeated histological examinations have failed to reveal lupous tissue. Calciferol has no bactericidal or bacteriostatic effect *in vitro* (24, 29, 35, 42), in animal experiments (4, 35), or in the organism. Wetherley-Mein (43) has shown that calciferol does not affect the growth, viability, or virulence of the lupus strains. As local calcification (38) is now supposed to be a secondary phenomenon, most workers regard the effect of calciferol as one of stimulating the

production of normal granulation tissue (7, 15, 16). Wetherley-Mein (52), who made detailed studies and pointed out the importance of Jensen's (13) demonstrations of the local action of calciferol, and Stringer's (36), discovery of the effect on experimental granulomas, arrived at the conclusion that the effect of calciferol is antituberculous and local, but with no influence on the growth, viability, and virulence of the tubercle bacillus. These views are all consistent with the explanation of the complications observed here. It is more difficult to account for the complications on the basis of the hypothesis of a *stimulating* effect on the production of normal granulation tissue. If, however, we suppose that the calciferol treatment causes shrinkage of the lupus tissue by direct cell damage or interference with the chemical properties of the tubercle bacillus, we have a satisfactory explanation. The view of calciferol as a cell poison has previously been advanced (34) and is not disproved by the histological picture (8, 40); it is supported, if anything, by the local ulcerative destruction observed by several workers (2, 31). The excessive destruction noticed by Lomholt as a response to combined treatment with calciferol and light is presumably accountable for by the added calciferol actions of the two methods. If this hypothesis is correct, the mechanism of the described complications is simply explainable as a liberation of tubercle bacilli from the lupus tissue with a chance of local recurrence or haematogenic spread. The picture is thereafter determined by the varying relation between the number and virulence of the tubercle bacilli and the resistance of the organism. Consequently, treatment with calciferol without simultaneous chemotherapy or treatment with antibiotics must involve a greater risk than previously realized, because the virulence-resistance relation is only imperfectly assessable in advance.

SUMMARY

During calciferol treatment of 284 patients suffering from lupus vulgaris six experienced reactivation of tuberculous processes and 37 fresh tuberculoid processes. In 36 cases (12.7 per cent) the treatment gave rise to a complicated course with two or more complications occurring at the same time. The complications were mostly of a benign nature, coming on about the time of subsidence of the lupus, bearing no relation to the dose of calciferol. The complications usually disappeared spontaneously when the treatment was discontinued or when the lupus had subsided. Renewed treatment of persisting lupus or treatment of recurred lupus generally gave rise to the same complications. Activation of pulmonary processes were twice observed three times in the same patient. In the cases of severe complications tubercle bacilli were demonstrated, with a single exception, whereas such were traced in only few of the cases with mild complications. Mild and severe complications occurred combined. Tuberculides and lung infiltrations came on in an age-class where they are otherwise rare. The tuberculin reaction before the calciferol treatment was weaker than in the total series, while freedom from relapse of lupus vulgaris was more frequent in the series of complicated cases. We may therefore be justified in regarding the majority of these complications as a consequence of calciferol treatment or subsidence of lupus vulgaris, though we do not know the incidence of similar complications in an untreated series.

The complications, which present a picture corresponding to haematogenic spread of tubercle bacilli, can be explained if we suppose that calciferol has an inhibitory or destructive influence on lupus tissue without affecting the virulence of the tubercle bacillus. In spite of the usually benign course of the complications, calciferol treatment of lupus vulgaris without simultaneous chemotherapy or treatment with antibiotics probably involves a greater risk than previously realized, because the virulence-resistance relation is only imperfectly assessable in advance.

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THE EFFECTIVENESS OF HYDROCORTISONE OINTMENT IN VARIOUS CUTANEOUS DISEASES

A CONTINUED STUDY

By BJØRN HEILESEN, AAGE KRISTJANSEN and FLEMMING REYMANN

In a previous report we have presented the preliminary results obtained in the treatment of various cutaneous diseases with hydrocortisone in ointment form. The marked therapeutic effect frequently observed in diseases like anogenital eczema, neurodermatitis, atopic dermatitis, polymorphous actinic dermatitis, various types of chronic eczema and several other cutaneous lesions made us regard this method as a significant advance in dermatologic therapy, not the less so because a large proportion of these patients are refractory to conventional therapy. It was stressed, however, that further experience would be required to assess the duration of results. 12 months have now elapsed since the inception of this study, and the reaction of these chronic cutaneous diseases to long term hydrocortisone therapy will be discussed in the present paper.

Our results are largely in conformity with those reported in the literature, and there is general agreement that the therapeutic effect of topically applied hydrocortisone is analogous to that obtained with its oral administration. On the other hand, we have not been able to find any reports of studys evaluating the possibilities of effecting a cure with long continued application of hydrocortisone ointment.

Experiences with ACTH and cortisone in the treatment of dermatologic disorders of the aforementioned categories indicate that the use of hydrocortisone ointment cannot be expected to provide actual cure except in a minority of cases. In ACTH and cortisone therapy the risk of serious side reactions is so high, however, that prolonged administration of these drugs in patients with cutaneous disease would be an exceptional procedure, and our experience with such long term therapy is therefore highly limited. With the use of hydrocortisone in ointment form a systemic effect and, hence, side reactions can be avoided, and large scale studies can safely be made to assess the effectiveness of continuous, long term application. The present study was designed specifically to determine whether prolonged application of hydrocortisone ointment would be capable of curing diseases like anal pruritus, anogenital eczema, neurodermatitis and other lesions which apparently subside when the external stimulus, itching, is removed for some length of time.

Before presenting a detailed analysis of our results of therapy we shall mention the ointment base employed, a factor which has proved to be one of major significance. In the initial stages of our study we tried a number of different ointments, but we are now favouring and making exclusive use of an ointment of the following composition, prepared in the pharmacy of the Municipal Hospital, Copenhagen:

Hydrocortisone	cg 10
Glyceryl monooleate	cg 25
Vaselinum album	g 4.25
Adeps lanae	cg 50
Citrate buffer solution pH 5	g 5

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We employed hydrocortisone in alcohol form, as distinct from most commercial preparations which are made from hydrocortisone acetate. Comparative studies have been performed i. a. by Rein and Friedlaender & Friedlaender who found that the clinical effect of the two forms of hydrocortisone was the same.

The ointment base was chosen originally because experience had shown that it was tolerated even by the most sensitive patients in whom prolonged application of ointments of the carbowax and vaseline types was frequently seen to produce irritation. It will appear from the literature that several investigators (McCorriston, Sulzberger) have worked with various other ointment bases, as they were not entirely satisfied with the commercial ointments.

In the course of our study it became increasingly clear that the ointment base had a decided influence on the therapeutic effect; thus, exacerbation of cutaneous lesions was a frequent observation when our ointment was replaced by a commercial preparation. Our present knowledge of the properties of hydrocortisone in regard to solubility and resorption is too incomplete to offer a plausible explanation of this phenomenon, but there is experimental evidence of a marked difference in effectiveness of the various preparations. As a rule we employed hydrocortisone of the concentration 1 per cent, and in a small proportion of cases the therapeutic effect could be maintained with a concentration of 0.5 per cent. Especially American authors have frequently used higher concentrations (2.5—5 per cent), but for reasons of economy we had to refrain from that. However, we employed a concentration of 2 per cent successfully in a few recalcitrant cases.

Hydrocortisone ointment was applied in a thin layer morning and evening, and most patients needed no dressings.

As mentioned in our previous report, several control measures were carried out, especially in the early stages of our study, to rule out the ointment base as the factor responsible for the favourable results. Later on we confined ourselves to using only one control measure, viz. transition from hydrocortisone ointment to ointment base alone when a pronounced effect had been attained and, in the case of subsequent exacerbation, resumption of hydrocortisone.

RESULTS OF THERAPY

The majority of the patients were given ambulatory treatment. At the completion of the present study they were called up for re-examination and final evaluation of results. In the individual patient we distinguished only between essential effect and no effect, so that the patients who reported that there had been »some« or »perhaps some« effect were registered in the group showing no effect.

Anogenital eczema.

43 patients (24 women and 19 men) with this disease were treated, 14 of whom (9 women and 5 men) failed to respond to therapy.

3 women had kraurosis vulvae; 2 of these stated that there had been no relief of itching.

2 of 9 women with genital eczema alone reported no effect.

The remaining 31 patients had anogenital eczema; among these there were 27 (8 women and 19 men) with anal eczema of the chronic type. We took a particular interest in this group of patients because of the well known refractoriness of this disease to ordinary dermatologic therapy. On follow-up examination it appeared that none of the patients had been permanently cured. 5 had been symptom-free for some months (2, 3, 6, 3, 1) after discontinuation of therapy whereupon they developed relapses. In these patients the duration of therapy in months had been 4, 1, 1, 3 and 1 respectively.

Among the 27 patients with anal eczema an excellent but purely symptomatic response was seen in 4 of 8 women and in 14 of 19 men. The patients experienced objective as well as subjective freedom of symptoms as long as the ointment was employed, but when withdrawal was attempted, even after continuous application for 12 months, relapses occurred promptly or within a few weeks.

Cessation of itching within a few days was the normal rule in these patients, but lichenification and eczematous changes did often persist for several months before regression took place.

We found no relationship between duration of disease and therapeutic effect. The average duration of disease was 5.3 years in the 9 patients showing no improvement, as compared with 5.4 years in the 18 patients who became symptom-free.

Neurodermatitis.

This group contained 30 patients (19 women and 11 men).

As in the group with anal eczema, these were cases of long standing in which previous treatment by the generally accepted methods had produced little or no effect. The average duration of disease was 5.5 years.

5 patients (3 women and 2 men) failed to respond to therapy.

In the others there was prompt cessation of itching with subsequent, slow regression of often severe lichenification. On follow-up examination it was found that a lasting cure had been achieved in none of these patients of whom 19 had received continuous therapy over an average period of 4 months. 3 patients with an average duration of disease of more than 10 years became symptom-free after treatment for 2, 2 and 3 months respectively but developed relapses 6, 8 and 2 months after treatment. Several patients with

otherwise intractable neurodermatitis were treated continuously for 12 months but had prompt relapses when hydrocortisone was discontinued.

Atopic dermatitis.

As mentioned in our preliminary report, we took a particular interest in the treatment of this disease, partly because the favourable results obtained with ACTH or oral administration of cortisone provided a stimulus to experiments with local therapy, partly because ordinary dermatologic therapy has so relatively little to offer.

During the past 12 months we have treated 16 girls, 17 boys, 24 women and 14 men. To some extent these patients are representative of a selected material, as our interest was centred predominantly on the severe cases. On follow-up examination no effect was seen in 8 girls (50 %), 8 boys (47.1 %), 3 women (12.5 %) and 3 men (21.4 %). In other words, there was excellent effect in 51.2 per cent of the children and in 84.2 per cent of the adults.

In most patients the old, recognized method with tar produces regression of lichenification more rapidly than any other form of treatment, including hydrocortisone. Like all the other measures available for the treatment of atopic dermatitis, tar offers only symptomatic relief, however, and in the more severe cases relapses are sure to occur very soon after discontinuation of therapy. As our study progressed and we had been convinced that hydrocortisone was capable of producing a marked effect in patients with atopic dermatitis, we decided to treat hospitalized patients first with tar and then, when regression of lichenification was taking place, with hydrocortisone. Outpatients were given hydrocortisone exclusively.

Hydrocortisone proved effective within a few days, but when therapy was stopped, even after a period of months, there was often an equally prompt occurrence of relapse. All the patients have to use the ointment continuously, but many patients prefer this method to tar because the ointment is odourless, easy to administer and causes minimal soiling of clothes and linen.

The patients with more severe lesions could not be kept symptom-free with the use of hydrocortisone ointment, but itching was reduced to such an extent that their condition became tolerable.

It should be emphasized that complete involution was a rare occurrence in these patients.

Eczema.

This extremely heterogenous group consisted of 51 women and 19 men. The distribution of cases according to diagnosis is given below. Figures in parenthesis indicate the numbers of patients showing no response.

The patients with eczema sparsum reacted almost immediately, but here too hydrocortisone was purely symptomatic in effect. 2 men who had had recurrent eczema sparsum for 6 and 7 years respectively, for which every kind of dermatologic therapy had been tried, could be kept symptom-free as long as the ointment was used. Incidentally, one of them is about to be cured, but there are strong indications that in this patient it is a question of spontaneous healing.

Table 1.

Diagnosis	Women	Men
Eczema sparsum	3 (2)	6 (1)
» allergicum	8 (0)	4 (1)
» palpebrale	5 (1)	
» auriculare	5 (2)	2 (0)
» manuum	21 (6)	5 (1)
Other varieties	9 (2)	2 (1)

A similar, beneficial effect was frequently seen in the group with allergic eczema which comprised 12 patients, 6 of whom were hypersensitive to turpentine, 4 to nickel, 1 to chrome and 1 to perlon. With the use of hydrocortisone ointment these previously recurrent eczemas could be kept in abeyance even despite continuous exposure. As would be expected, however, hydrocortisone failed to prevent recurrence in the case of violent exposure.

Several of the patients with palpebral and auricular eczema of the chronic type presented histories of disease of several years' standing. None appeared to obtain a lasting cure, but 2 required only intermittent therapy.

The largest group was the one consisting of patients with non-allergic eczema of the hands; among these there was a number with chronic toxic eczema. In 21 cases the average duration of disease was 4.6 years; the others were of short duration and included 3 of the pustulous type which did not improve.

Polymorphous actinic dermatitis.

In 7 patients (5 women and 2 men) with polymorphous actinic dermatitis of mild to medium degree (all were symptom-free in the winter) hydrocortisone ointment was employed as the only therapeutic agent. As would be expected from the results reported in the spring of 1953, they all showed improvement of their lesions and cessation of itching after a few days of therapy, but the study also revealed the need for treatment throughout the summer months.

Pityriasis simplex eczematisata.

This group contained 20 patients (9 women and 11 men). The majority of cases were of long standing and had been resistant to previous therapy. In 13, an excellent response was obtained with the use of hydrocortisone ointment.

Striking features about ACTH therapy of this disease are the prompt response and the equally

prompt occurrence of relapse on withdrawal. Exactly the same type of reaction was noticed with topically applied hydrocortisone, but in a number of cases the lesions gradually subsided during therapy so that no further treatment was required after 1—3 months, mostly after the ointment had been applied every second or third day for some time.

This disease is apparently singular in that acute flare-ups attended by violent eczematization may occur during an otherwise successful course of therapy with hydrocortisone. We had that experience in 3 of 13 patients, but tolerance of hydrocortisone was restored after wet dressing etc. had been applied for some time. It is possible that such flare-ups are due to a reduction in local resistance to infections, but we are unable to offer any definite explanation.

Other cutaneous diseases.

Small numbers of patients with other cutaneous diseases were treated, almost all of them without effect. The diseases in question were cheilitis (1 patient), psoriasis (3), pemphigus vulgaris (1), pemphigus vegetans (1), palmo-plantar pustulosis (2), moniliasis (1), lichen planus (3), keratoderma climacterium (1) Darier's disease (1) and rosacea (3).

3 patients with hypertrophic lichen planus said that there had been some relief of itching, and in conclusion it should be mentioned that complete involution was seen in 3 of 13 patients with discoid lupus erythematosus. 2 of these were typical instances of the acute, pre-keratotic form. The third case, in which the diagnosis had been confirmed histologically, occurred in a boy aged 11 and had persisted for well over 6 months. None of these patients was cured after 6 months' continuous therapy.

DISCUSSION

Prior to evaluating our results with hydrocortisone ointment in the treatment of various cutaneous diseases it should be reemphasized that practically all the cases under review were chronic in nature and resistant to ordinary dermatologic therapy. The present therapeutic study, which extended over a period of 12 months, clearly showed that hydrocortisone ointment, like other therapeutic agents, was not capable of affording a cure, even when treatment was given continuously over a long period of time. Some of the patients were treated up to from 6 to 12 months. Pityriasis simplex eczematisata may be said to constitute an exception, but these cases do not pursue the same chronic course as, for instance, atopic dermatitis.

Most patients experienced prompt relapses when withdrawal of hydrocortisone was attempted, but even so we feel that hydrocortisone offers a definite advance in that it is capable of producing complete freedom or substantial alleviation of symptoms in patients with chronic cutaneous diseases. This may do much to alter the social destiny of many patients with atopic dermatitis who have hitherto been prevented from doing regular work or attending school because of itching and constantly recurrent eczematization.

In our experience the effect of locally applied hydrocortisone is comparable to that obtained with oral administration. Some critics have advanced the view that hydrocortisone is merely an excellent antipruritic, but our results in acute, eczematized atopic dermatitis as well as in pityriasis simplex eczematisata and allergic eczema clearly demonstrated the antieczematous effect of hydrocortisone ointment, reactions analogous to those following intracutaneous injection of hydrocortisone or systemic ACTH therapy. Further indications hereof were the prompt and acute flare-ups that were frequently seen after withdrawal of the ointment. As in systemic cortisone therapy, a blocking of the eczematous reaction was attained, but this blocking ceased as soon as therapy was stopped.

Our therapeutic results are summarized below:

Table 2.

	Number of patients	Number showing considerable improvement
Anogenital eczema	43	29
Neurodermatitis	30	25
Atopic dermatitis	71	49
Eczema	70	53
Polymorphous actinic dermatitis	7	7
Pityriasis simplex eczematisata	20	13
Total:	241	176 (73%)

It will be seen that 73 per cent of the cases showed considerable improvement; this is in accordance with the results reported i. a. by Sulzberger and Rein.

In addition to the cases shown in the table we have tried the hydrocortisone ointment in a limited number of patients with various cutaneous diseases mentioned above, but as could be expected they did not derive any benefit from the treatment and therefore they have not been included in the tabled cases.

In the case of many dermatologic therapeutic agents a lowered effect is often seen after some time of administration. We observed no such reaction to hydrocortisone, nor was such acquired resistance to be expected from the theoretical point of view.

As mentioned previously in this report, we have little knowledge of the properties of hydrocortisone in regard to solubility and resorption, and no definite explanation can therefore be offered

of the great difference of effectiveness of the various preparations. As in the case of cortisone we shall probably have to await the development of a radioactive hydrocortisone before we may obtain exact information on these points, and only then shall we be able to select the most suitable ointment base.

Several authors, Coste et al., Sidi et al., Sullivan et al., and Turell, have used intracutaneous injection of hydrocortisone for the treatment of various cutaneous lesions, for instance keloids, sarcoidosis and anogenital pruritus. We tried this form of therapy in a few recalcitrant cases of lichen planus, but the number of patients so treated is too small to allow definite conclusions of therapeutic results.

While the present study was in operation we employed hydrocortisone ointment as the only therapeutic agent in order to ascertain the potentialities of this new remedy. Increasing numbers of our patients are now receiving a combination of hydrocortisone ointment and ordinary dermatologic therapy, and we are treating for instance neurodermatitis and certain varieties of eczema of the hands with a combination of hydrocortisone and grenz rays. Moreover, as previously mentioned, we have obtained gratifying results in patients with atopic dermatitis who were treated first with tar and then with hydrocortisone.

The therapeutic results clearly showed that hydrocortisone was purely symptomatic in effect. The consequence of this must be that the ointment should not be used indiscriminately in the treatment of cutaneous diseases. Its scope of indication should largely be confined to the lesions mentioned in Table 2, and in these cases hydrocortisone should as a rule not be resorted to until other dermatologic methods have proved ineffective. Despite these limitations in the scope of indication of hydrocortisone, we feel that local therapy with hydrocortisone ointment represents a significant advance since it is possible by this method to induce freedom of symptoms or essential improvement in many patients with chronic cutaneous diseases.

SUMMARY

In a previous report we presented the preliminary results of the treatment of various cutaneous diseases with hydrocortisone ointment. The present paper is a discussion of the results of prolonged, continuous therapy which extended over a period of 12 months.

Essential improvement was seen in 29 of 43 patients with anogenital eczema, in 25 of 30 cases of neurodermatitis, in 49 of 71 cases of atopic dermatitis, in 53 of 70 cases of eczema and in 13 of 20 cases of pityriasis simplex eczematisata; 7 patients with polymorphous actinic dermatitis were all essentially improved.

It is pointed out that there is a decided difference in the effectiveness of various commercial hydrocortisone ointments.

Hydrocortisone ointment constitutes a valuable new addition to the methods of treatment of chronic cutaneous diseases when used either alone or in conjunction with ordinary dermatologic procedures. Hydrocortisone, which is purely symptomatic in effect, should be employed only in patients deriving no benefit from conventional dermatologic therapy.

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ESSENTIAL PULMONARY HAEMOSIDEROSIS

AN ACCOUNT OF TWO CASES, ONE TREATED EXPERIMENTALLY WITH ACTH

By ERIK SANDØE

Essential pulmonary haemosiderosis is a disease that occurs particularly in children and young adults. Judging from the literature, it is relatively rare. It was first described by Ceelen in 1930 (5) and since then only approximately 30 cases have been recorded (1—5, 7—25). As the name implies, deposition of haemosiderin in the lungs is concerned and the etiology is obscure.

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At autopsy, the lungs are found to be heavy, dark in colour and somewhat increased in consistence. Microscopic examination of the pul-

monary tissue reveals numerous macrophages filled with haemosiderin disseminated in the alveoli and parenchyma together with diffuse fresh haemorrhage. The capillaries are markedly dilated, tortuous and thick-walled. No breach of continuity is seen in any of the vessel walls, whether arterioles, capillaries or venules. Frequently, but not constantly, quite considerable degeneration of the elastic tissue and some fibrosis of the interalveolar septa are found. Apart from these findings in the lungs, only moderate changes are, as a rule, encountered. Depositions of haemosiderin, in particular, have never been demonstrated in the other organs. More or less pronounced hypertrophy of the right side of the heart may be observed together with slight hyperplasia of the spleen, and in 4 cases (5, 9, 11, 19) signs of myocardial lesion with round cell infiltration were found (in one of these, focal embolic nephritis was demonstrated in addition).

Clinically, the disease is characterized by prolonged anaemia of sideropenic type, by dyspnoea which is more pronounced than would correspond to the degree of anaemia and by recurring haemoptyses. In addition, many of the patients complain of attacks of uncharacteristic abdominal pain and, in connection with acute deterioration, slight jaundice is frequently observed.

Radiography of the lungs shows symmetrical diffuse, greyish veiling suggesting a membrane over both lung fields. This is most pronounced basally while the apices and hilar regions are most frequently unaffected. The changes are quite typical and the differential diagnosis from other conditions is, as a rule, easy. The constituent elements are nearly always much smaller than in miliary tuberculosis, Boeck's sarcoid and silicosis. In pulmonary haemosiderosis, developing as a result of chronic pulmonary congestion, distinct increase of the vessel markings is seen in addition to the membraneous veiling, while the vessel markings are normal in the essential form (22). The disease nearly always takes a chronic course with more or less prolonged remissions interrupted by acute exacerbations and after a duration of from one to several years, death often occurs suddenly with symptoms of acute copious pulmonary haemorrhage and rarely as the result of gradually increasing right-sided cardiac incompetence. Very little can be done therapeutically. By administration of iron, the anaemia may be improved or even cured but it does not seem possible to influence the tendency to pulmonary haemorrhage and the disease progresses to a fatal issue more or less independantly of the administration of iron.

In isolated cases, the diagnosis may involve difficulties. As mentioned, the anaemia may disappear during iron treatment; haemoptysis is, not uncommonly, absent, particularly in children; and the X-ray changes frequently do not occur until the disease has been present for a prolonged period. In dubious cases, the stomach washings should be examined for heart failure cells. Should this examination yield negative results, the diagnosis may be verified by biopsy of the lung (2, 10) but it should be borne in mind that such an intervention is not without risk and on account of the inadequate therapeutic measures available in these cases, it only serves a diagnostic object.

In the course of the past 6 years, two patients have been admitted with essential pulmonary haemosiderosis to the Medical Department of Frederiksborg County Central Hospital, Hillerød.

CASE-HISTORIES

Case I. Female, who died aged 25 years.

In the course of her life, she was repeatedly admitted to hospital. From the case-histories of the various hospitals, the following facts appear:

The patient had repeated attacks of tonsillitis, the last being 4 years prior to her death. Menstruation had been somewhat irregular but at no time particularly copious. Since her childhood, she had suffered from periods of fatigue and tendency to giddiness. In the last 6 years, she nearly always felt tired and out of form and was troubled by dyspnoea on exertion and tightness in the chest. Repeated expectoration of red lumps. During the last 4 years, she could only manage the most necessary work in the house with difficulty and in the last 3 years, she had repeated prolonged attacks of violent tachycardia. She died suddenly at home. Autopsy was not carried out.

At no time were definite pathological changes found on stethoscopic examination of the lungs and no murmurs were heard over the heart. The haemoglobin percentage was determined first when the patient was 9 years old and was then 80, but on examination one month later it was found to be 63 per cent. It was determined again at the age of 13 years and was then 64 per cent. (increasing to 82 per cent. during iron therapy in the course of a month). The haemoglobin was again determined when the patient was 19 years old and found to be 60 per cent. (increased to 97 per cent. during iron therapy). In the last 3 years of life, during which the patient probably received iron medication constantly, the haemoglobin fell only once under 70 per cent. and was, as a rule, between 80 and 100 per cent. The serum iron was determined repeatedly in the course of the last 4 years. It varied greatly but was, as a rule, between 0.040 mg.% and 0.080 mg.% but occasionally values as low as 0.011 mg.% and as high as 0.137 mg.% were recorded. Radiography of the patient's lungs was first undertaken when she was 13 years old. According to the description this revealed normal conditions. At the age of 19, she was X-rayed again. On that occasion, slight veiling of the lower half of the right lung field was reported. On control examination 3 weeks later, this had disappeared. Renewed X-ray examination 2 years later showed diffuse, symmetrical, finely spotted marking of both lung fields while the apices, hilar and sinus regions on both sides were unaffected. This picture remained more or less unchanged on repeated control radiography during the last 4 years of the patient's life. The contours of the heart appeared normal on all examinations and no increased vessel marking was found. The first electrocardiogram was recorded 4

years prior to the patient's death. On that occasion, normal conditions were found but 2 years later, left bundle-branch block plus ventricular extra-systoles were demonstrated and 3 months prior to the patient's death, alternation between nodal rhythm with left bundle-branch block and ventricular tachycardia was observed. Antistreptolysin titre was determined twice 4 years prior to the death of the patient with an interval of 3 weeks; in the interval between 2 determinations, the patient sustained an acute febrile tonsillitis; the first determination was 100 and the second 400. Tubercle bacilli could not be demonstrated on repeated cultures from the sputum. Mantoux 1:100 was found to be positive 4 years prior to death.

Summary: The patient was a female who died at the age of 25 years. She suffered from tonsillitis on repeated occasions and during the last attack of tonsillitis, about 4 years prior to her death, the antistreptolysin titre increased from 100 to 400. From the age of 9 years, she was admitted repeatedly to hospital with anaemia which disappeared on every occasion during iron therapy. In the last 6 years, she complained frequently of fatigue, expectoration of blood-stained lumps, tension in the chest on exertion and was nearly always troubled by quite pronounced dyspnoea on exertion. In the last 3 years, during which she received iron almost continually, the haemoglobin percentage was over 80 most of the time but the symptoms recorded remained unaltered in intensity. Repeated radiographs of the lungs showed definite pathological changes first 4 years prior to her death. A finely spotted veiling over both lung fields, most pronounced basally, was then seen and this picture remained more or less unaltered on repeated control radiography in the following years. On no occasion was it possible to demonstrate tubercle bacilli in the sputum. In the last 2 years, the patient was greatly troubled by prolonged attacks of palpitations and the electrocardiogram, previously normal, changed in the same period and showed left bundle-branch block and finally alternating nodal rhythm with bundle-branch block and ventricular tachycardia. The heart showed normal contours on all X-ray examinations and no murmurs were demonstrated on stethoscopic examination of the heart. The patient died suddenly in her home and autopsy was not carried out.

Case II. A boy, aged 16. Father died from bilateral pulmonary tuberculosis. His mother and sister do not seem ever to have had symptoms of anaemia. On an examination they showed normal haemoglobin percentages somewhat low serum iron (0.059 mg.% and 0.060 mg.%) and X-ray photographs of their lungs showed normal conditions. At the age of 10 years, the patient had pulmonary tuberculosis and was admitted to a sanatorium. X-ray of lungs: infiltration in right mid-field; stomach washings: tubercle bacilli +; haemoglobin 90 per cent.). Thereafter, the patient felt completely well for some years but during the last 3 years, for periods of a month's duration with intervening periods varying from weeks to months, the patient was troubled by dyspnoea on exertion and fatigue and, now and again, attacks of quite violent stabbing pain under the left costal margin. He was admitted to this Department for the first time 2 years ago. On admission, he was somewhat pale with slight dyspnoea at rest. On stethoscopic examination of the heart, a harsh systolic murmur was heard over the entire precordium without any definite point of maximal intensity. Stethoscopic examination of the lungs showed normal conditions. Haemoglobin percentage was 42, colour index 0.74, serum iron 0.036 mg.%, serum bilirubin 1.1 mg.% and reticulocyte count 3,5 per cent. X-ray of the lungs showed normal conditions. He was treated with iron orally for 1½ months, and during this period the haemoglobin percentage increased to 99. The patient was then discharged and advised to continue medication with iron at home (he probably did not adhere strictly to this advice). After discharge, he felt well for some months but then again began to feel tired and poorly and 6 months later he was readmitted. On admission this time he seemed to be slightly more dyspnoeic than on the first occasion. Stethoscopic examination of the heart and lungs showed unaltered conditions. The haemoglobin percentage was 52, the colour index 0.87, serum iron 0.046 mg.%, serum bilirubin 2.27 mg.% and, as previously, 3.5 per cent. reticulocytes were found. X-ray of the lungs now showed distinct changes, a diffuse membraneous veiling being seen over the lower $^2/_3$ of both lung fields; this was composed of miliary, partly confluent infiltrates, the size of pin heads. The upper lung fields and the regions of the hili were clear. The contours of the heart and the vessel markings were normal and an electrocardiogram showed normal conditions apart from slightly raised P-waves in leads II and III. Further examination of the heart and lungs, including catheterization of the heart and pulmonary function tests led to the conclusion that the patient's dyspnoe was purely of pulmonary origin. No tubercle bacilli could be demonstrated in repeated stomach washings. Mantoux 1:100 was positive. Microscopic examination of a sligthly enlarged lymphatic gland showed simple hyperplasia. An attempt to remove a paratracheal gland by Daniel's method (6) was unsuccesfull, the tissue removed being devoid of lymphoid structures. The reaction for toxoplasmosis was positive (neutralization reaction positive in dilution 1:1250, complement fixation reaction in 1:4). Numerous other laboratory tests were performed but all showed normal conditions.

Shortly after admission, iron administration was commenced both intravenously and orally and in the course of the following 6 weeks, the haemoglobin percentage increased from 52 to 99. Two months later, the patient's condition deteriorated. He began to expectorate dark red lumps of sputum, the dyspnoea became more pronounced and the changes in the X-ray pictures of the lungs increased. The haemoglobin percentage remained unchangedly high (iron was administered continuously).

Microscopic examination of the sputum revealed myriads of heart failure cells.

The diagnosis of essential pulmonary haemosiderosis was then regarded established and based on a hypothesis which will be accounted for later in this paper, therapy with ACTH: Acton Prolongatum (Frederiksberg kemiske Fabrik) was initiated.

For the first 4 months, the patient received both iron (ferrosi tartras 1.5 gm. daily) and Acton Prolongatum (20 units every alternate day) and thereafter for the past 2½ months only Acton Prolongatum (still 20 units every alternate day).

While the patient still received iron, he felt well. The dyspnoea seemed to be subsiding and he could carry out physical work to an extent which had been impossible for him during the past 3 years. The haemoglobin percentage remained about 100, while the serum iron fell from 0.087 to 0.065 mg.%. He con-

tinued to expectorate small bloodstained lumps at intervals of some days and the X-ray picture of the lungs remained unchanged. In the past 2½ months during which the patient did not receive iron, the haemoglobin percentage fell from 105 to 51 per cent., the serum iron from 0.065 to 0.030 mg.% but the changes in the X-ray picture of the lungs have not evidenced any sign of progression and the haemoptyses have not increased in frequency.

During treatment with ACTH, the patient developed a slight »moon-face« and quite pronounced acne of the face but the 17-ketosteroid excretion in the urine had only increased from 4.4 mg./24 hrs. to 5.4 mg./24 hrs.

Summary: A boy, aged 16 years. At the age of 11 years he sustained pulmonary tuberculosis which now appears to have been healed for a long time. During the past 3 years, he was troubled for long periods by dyspnoea on exertion, fatigue and pain under the left costal margin. He was admitted to this Department for the first time just under 2 years ago with sideropenic anaemia which disappeared rapidly during iron therapy. X-ray of the lungs showed normal conditions at this time. Nine months later he was readmitted on account of recurrence of the symptoms. Sideropenic anaemia was again found but X-ray of the lungs now showed symmetric veiling composed of miliary infiltrates over the lower $^2/_3$ of both lung fields. Examination of the heart, including cardiac catheterization showed normal conditions and no tubercle bacilli could be demonstrated on culture from the stomach washings. During iron medication, the haemoglobin percentage rose rapidly to normal values but the dyspnoea on exertion improved only to a slight extent. Two months later, he began to cough up red lumps, he became more dyspnoeic and an X-ray photograph revealed that the pulmonary changes had increased. The haemoglobin percentage remained high (he received iron continually). Microscopic examination of the sputum revealed myriads of heart failure cells and the diagnosis of essential pulmonary haemosiderosis was therefore regarded as established. Therapy with ACTH was thereafter instituted. During the first 4 months he received both ACTH and iron and thereafter ACTH solely for 2½ months. While the patient still received iron he felt well and the haemoglobin and serum iron remained relatively high. In the past 2½ months, during which iron has not been administered, both the haemoglobin and the serum iron have fallen markedly and the patient has felt tired and somewhat more dyspnoeic than proviously. The changes in the lungs have remained more or less unchanged during the past 6 months and the haemoptyses do not seem to have increased or decreased in frequency.

DISCUSSION OF THE AUTHOR'S CASES

The case-histories are quite characteristic, and the diagnosis seems to be clear in both cases. It must be regarded as highly probable that the myocarditis which occurred in the first patient was only an incidental complication. The fact that the haemosiderosis had produced symptoms for several years before the attacks of tachycardia commenced and before electrocardiographic changes appeared, together with the repeated attacks of tonsillitis and the increased antistreptolysin titre are evidence to support this. It should, however, be borne in mind, that myocardial injuries have also been demonstrated in other patients with essential pulmonary haemosiderosis (5, 9, 11, 19).

DISCUSSION OF THE PATHOGENESIS AND ETIOLOGY OF THE DISEASE

From comparison between the clinical and post-mortem findings it seems highly probable that the deposition of haemosiderin occurred as a sequel of recurrent diffuse haemorrhages due to diapedesis via the capillaries of the lungs and that the anaemia is secondary to the iron loss due to the deposition of haemosiderin.

Very little is known regarding the cause of these haemorrhages. Strikingly marked dilatation of the pulmonary capillaries is constantly encountered and many authors record simultaneously pronounced degeneration of the elastic tissue (5, 11, 20, 24, 25). Some of them (5, 11, 20, 25) have therefore assumed the primary disease to be hypoplasia of the elastic tissue in the lungs. According to Glanzmann et al. (11), this produces stasis of blood in the pulmonary capillaries which, in its turn, is presumed to be the immediate cause of the haemorrhages. Records of post-mortem examinations are, however, available in which the elastic tissue in the lungs was found to be intact (3, 15, 18, 19) and as, in addition, in pulmonary haemosiderosis occurring as a result of chronic pulmonary stasis, degeneration of elastin of the same nature as that found in the essential form is quite frequently encountered, it seems reasonable to assume that the changes in the elastic tissue in both types of pulmonary haemosiderosis are secondary to the deposition of haemosiderin.

Nancekievill (15) suggests that the haemorrhages occur as a result of increased pressure in the pulmonary circulation. Constantly increased pressure does not seem to occur as only rarely excessive right-sided hypertrophy of the heart is encountered even in patients in whom the condition has been present for several years. Furthermore the cardiac catheterization in the second patient showed normal conditions of pressure in the right side of the heart and in the pulmonary artery. The other possibility that acute pulmonary stasis is occurring in attacks as a sequel of periodic flaring up of a latent myocarditis is contradicted by the fact that pulmonary oedema has never been described in these patients.

Gellerstedt (9) and Scheidegger et al. (19) suggested that an infectious-toxic condition is possibly involved as they have attached particular significance to those cases in which signs of myocarditis or nephritis were found simultaneously.

It seems to me most probable that an allergically conditioned pulmonary purpura is concerned, as first mentioned by Wiesman et al. (24), i. e. a condition which may be compared with bron-

chial asthma (perhaps this condition may best be expressed by employing the term "haemorrhagic asthma" concerning essential pulmonary haemosiderosis). This hypothesis is the only one which simultaneously offers a really good explanation of the pronounced capillary dilatation and of the intermittent course of the disease, but it must be admitted that positive observations are otherwise lacking to support this hypothesis. In particular, nothing is known concerning the factors that release the assumed allergy.

The hypothesis mentioned last induced me to treat my second patient with ACTH. As described, there was apparently no definite effect.

SUMMARY

As an introduction, a brief description of the clinical and pathological findings in essential pulmonary haemosiderosis is given. The author reports 2 new cases of the disease and discusses its etiology and pathogenesis. He compares it with bronchial asthma and finds it most probable that localized pulmonary purpura on an allergic basis is concerned. From this presumption he treated one of his patients with ACTH. At the time when this paper went to press, the patient had been treated with the said preparation for over 6 months apparently without any great effect.

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THE CHANGES IN THE IMPORTANCE OF CERTAIN CAUSES OF DEATH IN THE SCANDINAVIAN COUNTRIES

By MARIE LINDHARDT

Each of the three Scandinavian countries Denmark, Norway and Sweden forms a separate kingdom. There is no difference between them as to race, culture or faith, and in language and social conditions they are also very close. The populations in 1950 were 4.3 millions in Denmark (D.), 3.3 millions in Norway (N.) and 7 millions in Sweden (S.). The only foreign elements in the population live in the most northerly regions of Norway and Sweden (30,000 Finns and 10,000 Lapps). Their relatively small numbers have little effect on the statistics of death causes. Denmark's area, however, is only 43,000 square kilometres, whereas Norway and Sweden, stretching far up to the north, have 324,000 and 449,000 sq. km. respectively.

Roughly speaking, medical training in the three countries is the same, and I have considered it justifiable to conclude that their diagnoses are comparable. 11 causes of death for which the diagnoses specially are likely to have been reasonably uniform in each country for the 30 years period 1921—50 have been selected — with a few exceptions for Sweden. In the northern parts of Norway and Sweden, however, where the population is very thinly scattered, medical death certificates have had to be dispensed with in more cases than in Denmark.

The 11 causes of death are not those with the highest frequencies, cf. the table, but have been selected partly because they have undergone some

From the Danish National Health Service.
Paper read at the World Population Conference in Rome 31 August — 10 September 1954.

Table 1.
The occurrence of certain causes of death in Denmark, Norway and Sweden 1921/25 and 1946/50.

	Denmark				Norway				Sweden			
	1921/25		1946/50		1921/25		1946/50		1921/25		1946/50	
	Annual av. actual	% of total deaths	Annual av. actual	% of total deaths	Annual av. actual	% of total deaths	Annual av. actual	% of total deaths	Annual av. actual	% of total deaths	Annual av. actual	% of total deaths
Tub. of respiratory system	2,361	6.25	834	2.14	4,197	13.45	1,255	4.29	7,113	9.85	2,303	3.27
Tub. of meninges and central nervous system	404	1.07	58	0.15	636	2.04	96	0.33	786	1.09	94	0.13
Nephritis, acute and chronic	679	1.80	478	1.22	699	2.24	512	1.75	1,478	2.05	1,105	1.57
Ulcer of stomach and duodenum..	125	0.33	341	0.87	174	0.56	162	0.55	596	0.82	457	0.65
Cancer of stomach	1,711	4.53	1,483	3.80	1,536	4.92	1,591	5.44	—	—	—	—
Cancer of breast..	293	0.78	610	1.56	145	0.46	314	1.07	341	0.47	768	1.09
Cancer of uterus..	320	0.84	459	1.18	187	0.60	245	0.84	—	—	—	—
Cancer of lung....	—	—	380	0.97	—	—	163	0.56	—	—	—	—
Heart diseases 25—54 of age	601	1.59	822	2.10	532	1.70	455	1.56	1,246	1.72	928	1.32
Accidents	1,037	2.75	1,747	4.47	963	3.09	1,477	5.05	2,081	2.88	2,614	3.72
Suicide	462	1.22	1,039	2.66	155	0.50	215	0.73	869	1.20	1,045	1.49
Altogether	7,993	21.16	8,251	21.12	9,224	29.56	6,485	22.17	14,510	20.08	9,314	13.24
Total deaths	37,751		39,061		31,211		29,254		72,244		70,348	
Total deaths per 1,000 population	11.25		9.33		11.52		9.15		12.05		10.23	

form of change in the period, partly for the reason that they comprise only a relatively small number of elderly people, in whom the actual cause of death may be difficult to ascertain because there is often a complex of diseases, all of which have contributed to the death of the person.

Until 1926, when the three countries agreed upon a joint inter-Scandinavian death-cause nomenclature, based essentially upon the international one, each country made use of her own local disease groups. In 1927 Norway, and in 1931 Denmark and Sweden adopted the inter-Scandinavian nomenclature; Sweden continued to use it right up to 1951, when all three countries adopted the international Classification of 1948, whereas Denmark and Norway went in for the international one as from 1941.

The marked decrease of *pulmonary tuberculosis* during recent decades is a familiar phenomenon in all civilized countries. The individual placing of the three countries has been more or less the same, Norway being highest, Denmark lowest and Sweden midway between, cf. fig. 1. One curious circumstance, however, is common to all three: In the years up to the Second World War, mortality among males was lower than among females, but then the picture was reversed and now females in the three countries have the lower mortality. The change began as early as in 1934 in Norway, and not until 1939 in Sweden and 1940 in Denmark.

The decrease of pulmonary tuberculosis on the whole has been heaviest among females and in the young age-groups, that is to say where conditions used to be worst. The big drop among children in recent years may presumably be credited to BCG vaccination. The well-known peak on the curve of tuberculosis mortality in the age-group 15 to 30 years has been flattened and mortality among males of over 45 years is now higher than among young males and females in what was once »the dangerous age«.

There are various reasonable explanations of this: The increasing industrialization in some of the countries at the expense of agriculture may perhaps mean that males, who as experience shows are particularly exposed to infection in large industrial centres, cannot participate in the general decrease to the same extent as females. Another possibility is that females, whose occupation in trade and industry has been strongly on the increase during the last ten years, now through their increased earning capacity have helped to raise their own standard of living and that of their families so much that they can obtain better nutrition and on the whole become more resistant to infections. Finally, as regards females in the rural areas, there is the special circumstance that in former days, when tuberculosis was widespread among cattle, women helped in the milking of cows and may thus have been exposed to infection with bovine tuberculosis; nowadays, bovine tuberculosis has declined remarkably, and it is only at few places that females do the milking.

For some years tuberculous *meningitis* shared in the general decline of tuberculosis, cf. fig. 2. The heavy decrease during the last 6 to 7 years

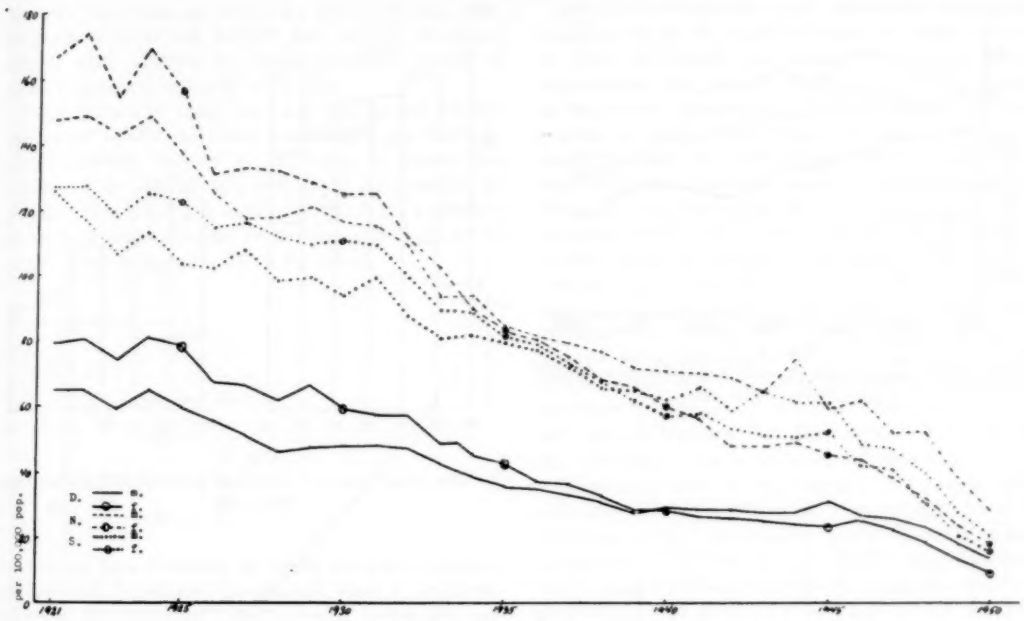

Fig. 1.
Deaths from pulmonary tuberculosis per 100,000 population 1921—50.

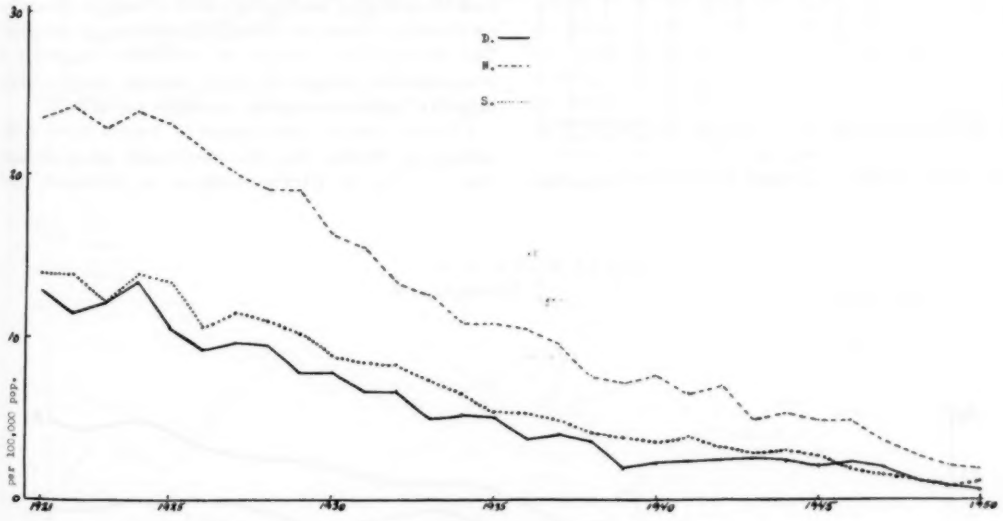

Fig. 2.
Deaths from tuberculou meningitis per 100,000 population 1921—50.

is due to Streptomycin, and possibly to BCG vaccination. The mortality is now at a minimum, about one per 100,000 in all three countries.

The decline in the mortality of *acute and chronic nephritis*, cf. fig. 3, must be considered in connection with the treatment of scarlet fever.

It is, however, a fact that Scarlatina mortality had started to decline before the introduction of penicillin therapy. The decline in mortality of Nephritis therefore cannot been aschribed to penicillin therapy only.

Among the *cancer* deaths, *cancer of stomach* has the highest mortality, cf. fig. 4; during the past few years cancer of breast among females in Denmark has got up to almost the same level. In cancer of stomach the diagnosis *may* be somewhat uncertain, as practitioners if patients die at home and thus escape the more definitive diagnoses of the hospitals, may be inclined to write cancer ventriculi on the death certificate in doubtful cases when the patients are old people. It being assumed difficult in some cases to diffe-

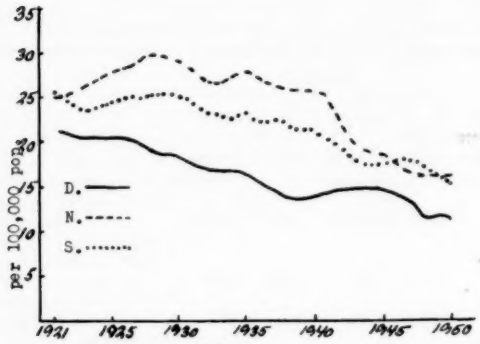

Fig. 3.
Deaths from acute and chronic nephritis per 100,000 population 1921—50.

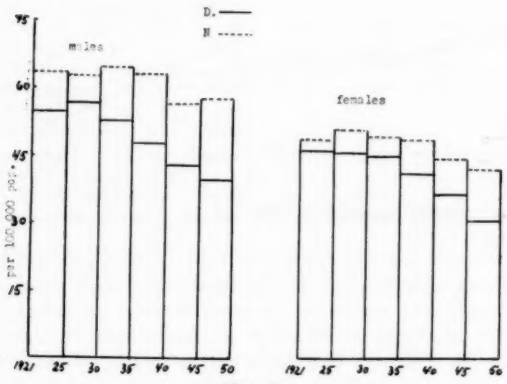

Fig. 4.
Deaths from cancer of stomach per 100,000 population 1921—50.

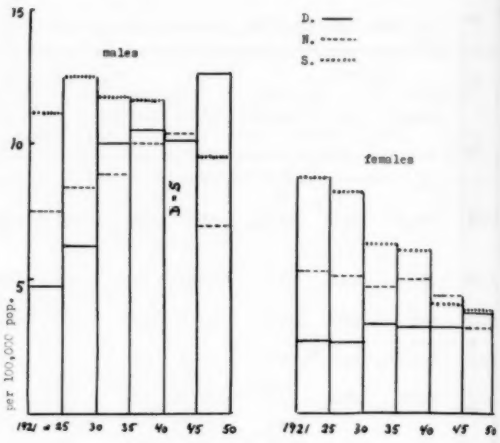

Fig. 5.
Deaths from ulcer of stomach per 100,000 population 1921—50.

rentiate between *ulcer of stomach* and cancer of stomach, I have tentatively included the figures for the latter disease too. The relatively marked increase in the mortality of ulcer of stomach, cf. fig. 5, observed among males in Denmark in the past decade has no counterpart in either Norway or Sweden where the disease is rather decreasing. The figures for cancer of stomach, showing a considerable preponderance among males, have actually been decreasing steadily since 1931.

Uterine cancer and cancer of breast have both increased during the 30 years, but at different rates, cf. fig. 6. Uterine cancer in Denmark and

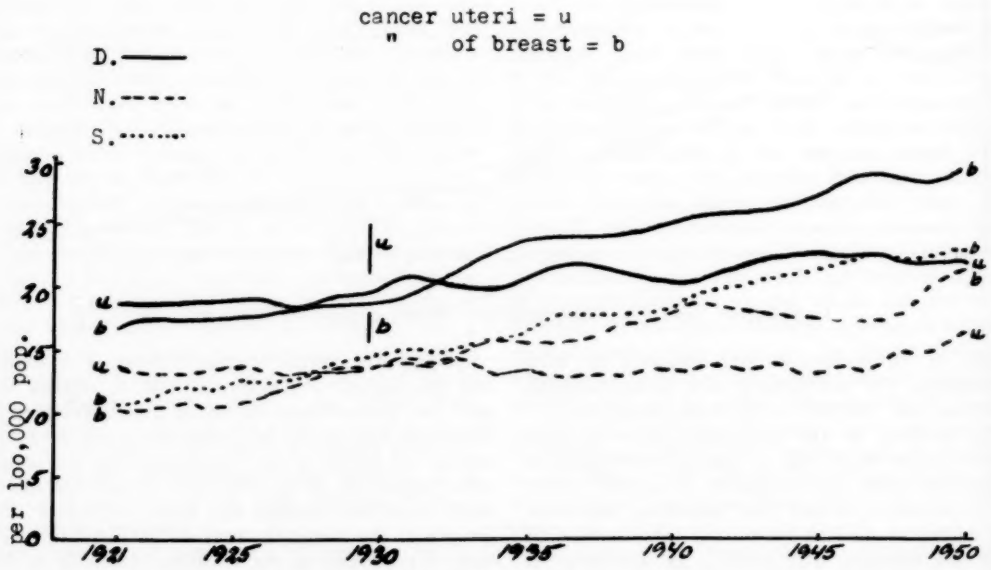

Fig. 6.
Deaths from cancer of breast and uterus per 100,000 females 1921—50.

Norway has only increased by about 10 per cent., whereas cancer of breast has almost doubled, which also applies to Sweden. Both forms of cancer increase rapidly with age.

Cancer of the lung was not segregated in the causes of death statistics until 1931. In Norway and Denmark cancer of the lung in males has increased by about 400 per cent. since 1931, in females about 100 per cent., cf. fig. 7. Its mortality is highest among males in the age-group 55 to 74 years, among females 65 to 84 years.

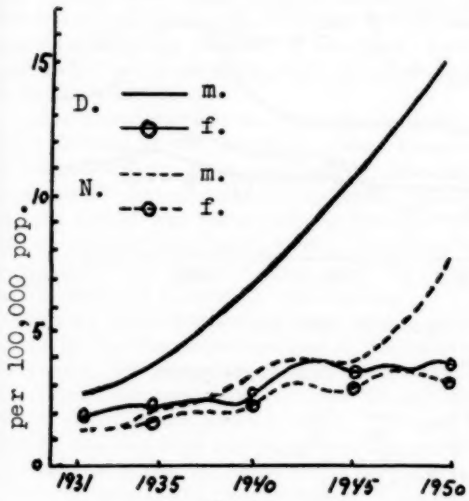

Fig. 7.
Deaths from cancer of lung per 100,000 population 1931—50.

Suicide is nowadays only registered under that heading when the cause of death is quite certain. In cases of doubt the deaths are placed under »accident«. The suicide frequency differs greatly in the three countries, but everywhere the frequency is highest for males, cf. fig. 8. Denmark stands highest for both males and females, Norway holds the most favourable position and Sweden is midway between, but nearer Denmark than Norway. The war years, when Denmark and Norway were occupied by German troops, caused a heavy increase in Denmark for both sexes, with the culmination in the first post-war years. The increase was relatively highest among females, who in 1945 had almost as many suicides as the males. In the past few years the suicide frequency has been on the down grade in Denmark, especially among females, but Denmark is still among the countries with a very high frequency.

In former days it was mostly old people who took their lives, but the past few decades in Denmark have recorded a fairly heavy increase in the age-group under 45 years, a slight increase between 45 and 74, and practically stagnation among the old of more than 75 years. In Norway the suicide frequency throughout the entire period of 30 years for both sexes was highest in the age-group 45 to 74, with but little fluctuation in this or other groups. For Sweden, the figures reveal an increasing trend in the suicide frequency among young women and a decrease among elderly males.

In Denmark, where hanging was the favourite method among males at the beginning of the period, poison is now chiefly resorted to by them,

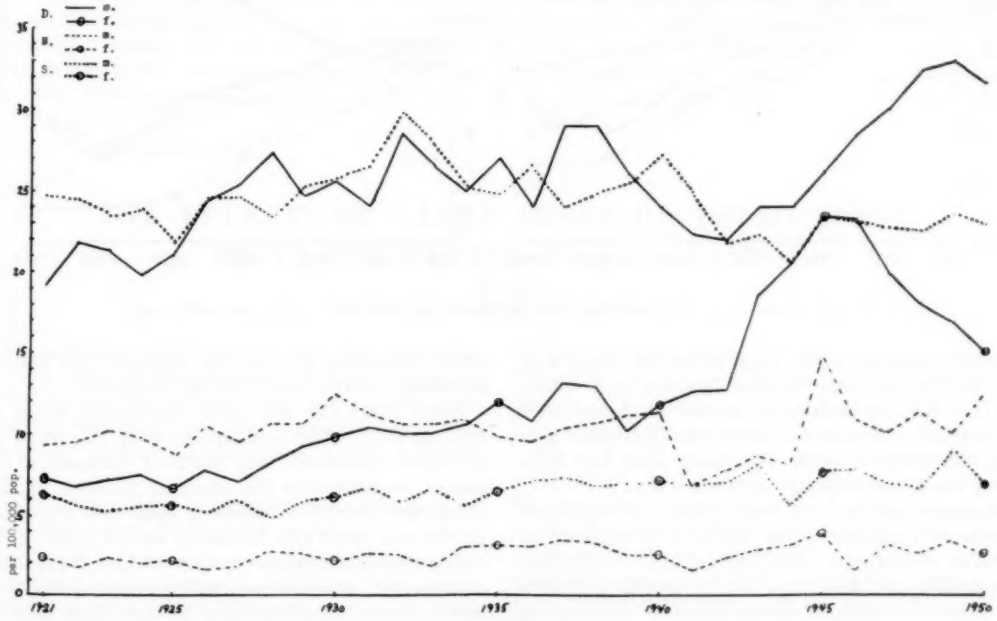

Fig. 8.
Suicidal deaths per 100,000 population 1921—50.

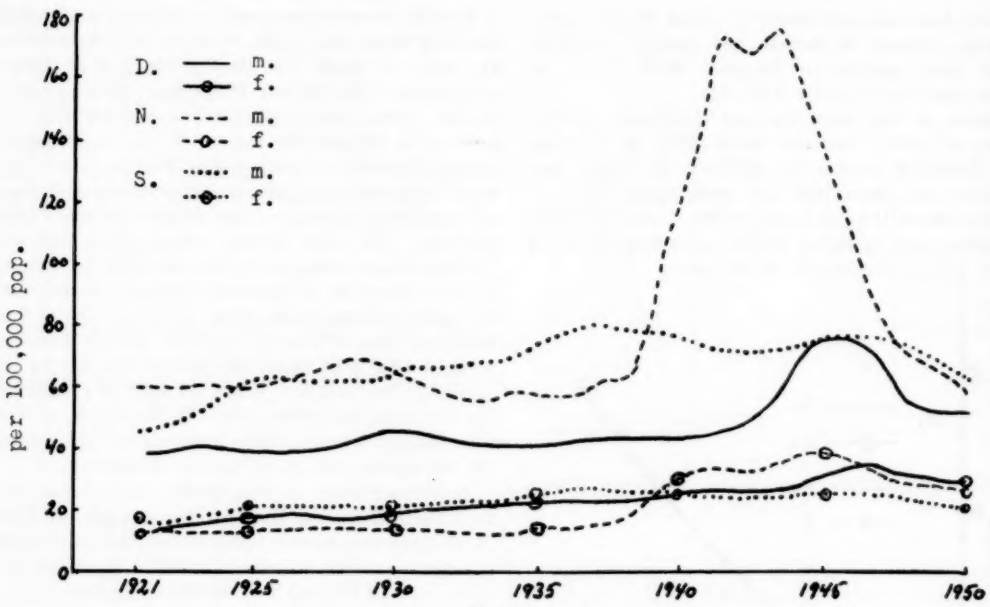

Fig. 9.
Accidental deaths per 100,000 population 1921—50.

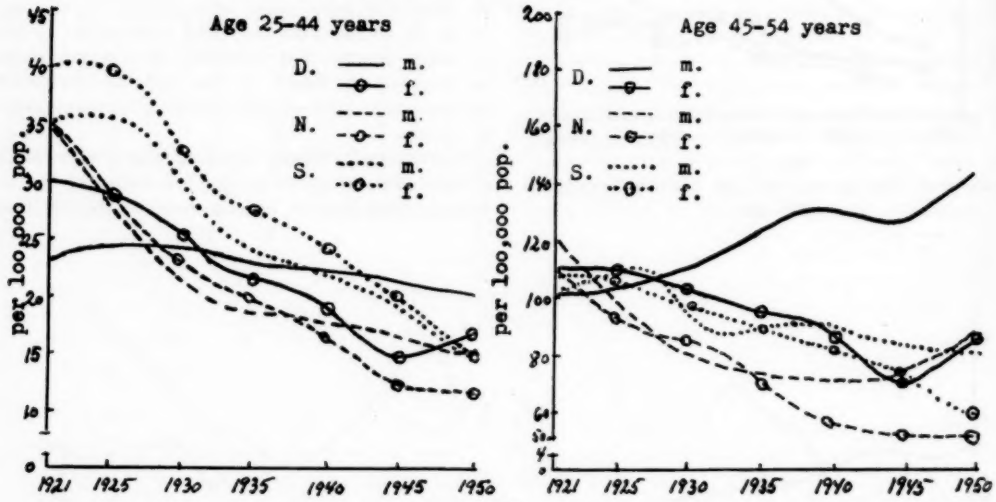

Fig. 10.
Deaths from heart diseases age 25—54 years per 100,000 population 1921—50.

whereas females have long preferred that way out. In Norway and Sweden, hanging and shooting are the methods used mostly by males and drowning by females; in these two countries poison still plays a relatively small role, but it is being used increasingly by both sexes.

Comparisons between *accidents* in different countries must always be made with reserve, as natural conditions, war, occupation, traffic etc. are hardly ever the same. The accident mortality in a period when total mortality is decreasing, and when large disease groups such as infectious diseases and others susceptible to the new therapeutic remedies are on the decline, will take a relatively greater share in the mortality.

Apart from the war and occupation years of 1940 to 1945, when conditions were abnormal in all three countries, the accident frequency for males lies highest in Norway and Sweden, cf. fig. 9, but the difference between these two countries on the one hand and Denmark on the other, once rather great, is now narrowing and in 1950 it was quite small. Accident mortality among females is much lower but is inclined to rise, especially in Denmark.

Children under one year, especially in Den-

mark, are very subject to die an accidental death, and the mortality among girls of this age is exceeded only by the high age-groups of over 65 years. Remarkably enough, even among infants, just as one might expect the case to be among the other ages, the male sex has the highest mortality. For the rest it is the occupational accidents and traffic accidents that stand out among younger males, whereas among the old it is especially the femur fractures which often occur when a person falls or stumbles.

Among the occupational accidents, shipping and fishing have higher figures in Norway and Sweden than in Denmark. Not only is Denmark's merchant fleet the smallest of the three, but requirements as to documentation of these deaths is also stricter there.

I have experimentally analyzed the mortality of *heart diseases* in the relatively young age-group of 25 to 54 years. Here we find the interesting phenomenon that whereas the mortality originally in most places was higher among females, there was a change so that the frequency became higher among males, cf. fig. 10, exactly as in the case of the mortality of pulmonary tuberculosis.

The time when the change occurred has varied a little in the three countries and in the different age-groups, but the movement is unmistakable: in the five year period 1946 to 1950 the mortality among males is everywhere higher than among females, whereas with few exceptions the opposite was the case at the beginning of the period. —

The decrease in the *total mortality* of the Scandinavian countries has been one of 10 to 15 per cent. during the 30 years. It was greatest in Denmark and Norway for females, and on examining the various age-groups we find an inprovement especially between 15 and 30 years, where the drop in mortality has been between 50 and 75 per cent. This is chiefly due to the lower tuberculosis mortality. Infant mortality in Denmark and Sweden — this latter country has by now the lowest infant mortality — has fallen by 70 per cent., but in Norway, which country had formerly a better position than Sweden, by about 55 per cent.

On the whole *age distribution* in the three countries is the same.

SUMMARY

Deaths from eleven causes capable of being diagnosed with reasonable uniformity in the three closely related Scandinavian countries have been analyzed for the thirty-year period 1921 to 1950.

Strongly declining mortality has been found for pulmonary tuberculosis, and a fall of almost the same dimensions is observable for tuberculous meningitis. Acute and chronic nephritis have also decreased.

Within the cancer group, cancer of stomach has steadily declined; cancer of breast has increased considerably, uterine cancer less so. There has been a violent increase in lung cancer, especially among males.

Ulcer of stomach has recorded a marked rise among males in Denmark.

Suicide and accident as causes of death have increased. These groups of death causes play a relatively increasing role gradually as it has become possible to combat other disease groups by medical means.

The suicide frequency is much higher i Denmark, whereas the accident figures, especially for males, are higher in Norway and Sweden.

Heart diseases in the age-group 25—54 years show that whereas at the beginning of the period females had the higher mortality, it is now much higher among the males. A corresponding change in the mortality of the two sexes has been found for pulmonary tuberculosis.

THE EFFECTS OF LARGE DOSES OF AMINO ACIDS ON EXPERIMENTAL POLIOMYELITIS

By CARSTEN RINDOM SCHIØTT

Attempts have been made to alter the intracellular formation of virus by changing the supply of amino acids, thus influencing the protein synthesis of the host cells. The methods used have comprised feeding the animals on a diet deficient in one or more amino acids (Davies et al.; Pond et al.; Kearney et al.), the injection or ingestion of amino acid analogues (Ainslie) and large doses of one or more amino acids.

Gershoff et al., in their experiments on mice, found that a surplus of methionine reduced the animals' sensitiveness to Lansing virus, the incubation and survival periods being prolonged. In order to obtain this effect it was necessary to commence treatment with methionine some time prior to infecting them with the virus. If the mice were put on a tryptophan deficient diet and given 6-methyl-tryptophan while being treated with

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This paper is part of a larger project concerning the effects of large doses of amino acids on protein synthesis carried out in cooperation with dr. *Niels Harboe* and with the support of The Danish State Research Foundation.

methionine, it was found that the protective effects were even more pronounced than where the substances were given separately.

Brown & Ackermann, on the other hand, discovered that Lansing virus in tissue cultures requires l-methionine, and that growth is retarded by dl-ethionine. Ainslie found that single injections of 150 mg of methionine-sulfoximine had inhibitory effects on Lansing virus in mice during the primary growth phase. Davies et al. observed only small effects of methionine deficiency on the course of poliomyelitis in mice; tryptophan and isoleucine deficiency, on the other hand, gave definite effects exhibited in the increased average incubation time. Kearney et al. and James et al. also found that tryptophan deficiency inhibited the propagation of Theiler and Lansing virus respectively. Experiments with, the tryptophan analogue 6-methyl-tryptophan, gave similar results.

In the following our experiments with various amino acids will be described. Previous to these experiments Harboe & Hansen had investigated the tolerance of mice towards the various amino acids employed.

TECHNIQUE

Mice: All the animals were males of the same strain, weighing 18—20 g. Standard diet and water were supplied ad libitum. The mice were fed each morning.

Virus: Casal's baby-mice adapted MEF-1 strain was employed. With the exception of the animals mentioned in table 2, the virus was injected as a $10 \div 2$ dilution of CNS, or approximately 100 x LD50. 0.03 ml was given intracranially in all cases. The mice were anaesthetized with ether.

Amino acids: The amino acids employed were commercial preparations from Hoffmann-La Roche. They were injected subcutaneously once daily, the first injection being given immediately following the virus inoculation. The substances were given separately to different groups of animals in the following doses: 0.5 ml each of dl-valine 60 mg/ml, dl-leucine 8 mg/ml, dl-phenylalanine 10 mg/ml, dl-alanine 120 mg/ml, dl-isoleucine 18.5 mg/ml and dl-tryptophan 4 mg/ml; 0.25 ml of dl-methionine 33 mg/ml, 0.2 ml of methoxinine* 40 mg/ml.

RESULTS

Table 1 shows the distribution of deaths with and without paralysis in 25 mice treated with methionine and in the control group. From these results it would appear that methionine facilitates the course of the infection to some extent, as more mice die exhibiting paralysis in the group given methionine than in the control group. The slightly shorter latency of paralysis and the reduced period of survival are hardly significant.

*) We would like to thank A/S Ferrosan who were so kind as to produce this especially for our investigation.

Table 1.
Mice Treated with 16,5 mg dl-Methionine per Day.

Days	Controls % † + P	Controls % † ÷ P	dl-Methionine % † + P	dl-Methionine % † ÷ P
2	0	8	0	4
4	4	24	12	12
6	8	32	24	16
8	32	40	60	20
10	48		68	
12	56		76	
14	60		80	
28	60	40	80	20
AOP:	7,1		6,4	
AST:	8,3		7,6	

% † +P: Cumulative per cent mice dead with paralysis.
% †+P: Cumulative per cent mice dead without paralysis.
AOP: Average interval to onset of paralysis in days.
AST: Average survival time in days.
Dilution of virus: $10 \div 2$.

Methoxinine apparently has no effect on the infection — at least not in the amounts used in this investigation (table 2).

Table 2.
Mice Treated with 8 mg Methoxinine per Day for 5 Days.

Days	Controls % † + P	Controls % † ÷ P	Controls LD 50	Methoxinine % † + P	Methoxinine % † ÷ P	Methoxinine LD 50
2	0	2,8	0,67	0	2,8	0,67
4	2,8	5,6	1,00	2,8	8,3	1,17
6	8,3	5,6	1,33	11,1	11,1	1,83
8	13,9	16,7	2,33	13,9	22,2	2,67
10	22,2	19,5	3,00	19,5	25,0	3,17
12	25,0	19,5	3,17	27,8	27,8	3,83
14	33,3	19,5	3,67	27,8	30,6	4,00
21	36,1	19,5	3,83	30,6	33,3	4,33
28	36,1	25,0	4,16	30,6	33,3	4,33
Surviving:	38,9 %			36,1 %		

Legends as in table 1.

Table 3.
Mice Treated with Different Amino Acids.

Days	Controls % † + P	Controls % † ÷ P	dl-Valine % † + P	dl-Valine % † ÷ P	dl-Tryptophane % † + P	dl-Tryptophane % † ÷ P	dl-Phenylalanine % † + P	dl-Phenylalanine % † ÷ P
2	0	10	0	10	0	0	0	0
4	0	40	10		20	10	20	20
6	0	50	30		20	20	20	20
8	30		60		60		30	30
10	40		90		80		60	30
12	50							40
14								
28	50	50	90	10	80	20	60	40
AOP:	7,4		5,8		5,8		5,5	
AST:	8,4		7,2		6,9		6,2	

Legends: as in table 1.

Valine, tryptophan, phenylalanine and leucine (table 3) have, as far as the first two substance are concerned, the same effects as methionine, i.e., a greater number of deaths with paralysis. AOP and AST seem to be somewhat reduced in these cases too.

Table 4.
Mice Treated with Different Amino Acids.

Days	Controls		dl-Alanine		dl-Iso-leucin		p-Amino-Phenylalanine	
	% † + P	% † ÷ P	% † + P	% † ÷ P	% † + P	% † ÷ P	% † + P	% † ÷ P
2	0	12	0	10	0	0	0	5
4	4	28	15	10	10	0	0	15
6	8	36	50	10	20	0	0	20
8	40	40	75	15	40	20	35	35
10	48	48	80		65	20	55	40
12	52					67	20	55
14					70	20	55	
28	52	48	80	15	70	25	60	40
AOP:	6,4		5,0		6,8		7,7	
AST:	7,4		6,1(7,4)*)		7,8(9,2)*)		9,0	

Legends: as in table 1.

*) One animal surviving more than 28 days.

With regard to alanine and isoleucine (table 4), their effects are the same as those of valine and tryptophan. However, one animal survived in both the alanine and isoleucine groups. If this animal is included in AST, the value given in parenthesis is found providing that the calculations are based on a period af 28 days. This experiment it has not been possible to reproduce, however. Even using smaller doses of virus, no increased survival tendency was observed. On the other hand, p-aminophenyl-alanine seems to inhibit the virus in its primary growth phase, and correspondingly the average length of survival is increased by 36 hours.

DISCUSSION

Davies et al. showed in their investigations of amino acid deficiency that the course of poliomyelitis was altered where there was a deficiency in valine, methionine, histidine, phenylalanine, leucine, threonine, isoleucine and tryptophan. In all cases the incubation period is lengthened and an increasing number of animals die without exhibiting paralysis.

The investigations reported here show corresponding conditions in that injections of amino acids gave an increasing number of deaths with paralysis, and a slight reduction of the length of incubation and survival. Gershoff found that methionine reduced the animals' sensitivity towards Lansing virus, whereas our investigations point more to there being an increase. However, in this connection it must be noted that injections of methionine were first commenced at the same time as the innoculations, while Gershoff gave methionine prior to infection.

No inhibition of the course of poliomyelitis has thus been observed, with the exception of cases treated with p-aminophenylalanine. This substance appears to inhibit the virus in the primary growth phase. In addition, it gives a slight increase in the average length of survival. However, the distribution of animals exhibiting paralysis on death is the same as in the control group.

SUMMARY

The course of experimental poliomyelitis (MEF-1) is investigated in mice that received large doses of the following amino acids from the day of infection: alanine, valine, leucine, isoleucine, methionine, tryptophan and phenylalanine. With the exception of phenylalanine, all the substances give an increased frequency of paralyses when administered separately. There is a slight reduction of the average incubation and survival periods.

P-aminophenylalanine seems to inhibit virus infection during the first week.

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BOOKS

THE MECHANISM OF LABOUR

By Erik Rydberg

New techniques have changed many an old concept. Sometimes the changes are revolutionary, sometimes they are mere modifications of old theories. Professor Rydberg's theory on the mechanism of labour might appear at the first glance to belong to the last group, because it seems so simple and self-evident that it does not strike one as something completely new, but it is a question whether it does not belong in the first group.

Traditionally, the term »mechanism of labour« covers only the mechanism of the foetal movements through the birth canal during delivery. The term is somewhat inadequate, because in the mechanism of labour in the strict sense the uterine forces, of which the foetal movements are only the result, is a factor at least as important as the foetal movements themselves.

For his very extensive studies of the factors which determine the foetal rotations through the birth canal Rydberg, who is the professor of Obstetrics and Gynaecology of the University of Copenhagen, has used roentgenograms of the foetal positions in the first part of labour and

motion-pictures of the foetus during delivery. Besides these clinical studies model experiments have been carried out. In these, wooden models of foetal heads were pushed in different ways with a sound or by means of compressed air through an elastic, cylindrical tube, bent so as to resemble the birth canal. All these studies and experiments are very thoroughly described and illustrated in the book, besides of course a detailed discussion of previous explanations of the mechanism of labour, from Smellie to the present days. Sellheim, whose theories have attracted great attention and have been of particular significance in modern obstetrical teaching, founded his arguments on the assumption that the foetal neck is not evenly flexible in all directions, and believed that the internal rotation of the foetal head is determined by this property. Rydberg has analyzed the shape of the foetal head and points out that it is bean-shaped with the bulk of its volume in front of the occipitomental diameter. He believes that it is the shape properties of the foetal head, which is the determining factor for the movements during labour. The importance of the shape of the head is clearly demonstrated in the model experiments, and since by dilatation the birth canal is transformed into a wide, bent tube displaying elastic properties, it is natural to assume that the shape properties of the foetal head have exactly the same significance during labour as the corresponding shape properties of the models in the experiments. The internal rotation is therefore explained as a movement of adaptation by which a minimum of tension in the structures subjected to deformation, the soft parts of the birth canal, is achieved.

The radiological studies of the position of the foetal head in relation to the pelvic inlet and the foetal body indicate that the so-called first rotational movement of the foetal head, the flexion, in the usual description of the mechanism of labour, is not a constant feature. It is shown that in most cases, no or only inconsiderable flexion of the head takes place until the lowermost part approaches the sacral tip and the internal rotation begins. The position of the foetal head is with other words pronouncedly constant during descent into the pelvic cavity in most cases.

In a final chapter the author develops a mathematical analysis of the model experiments. This, however, should discourage nobody from reading the book, because the experiments are so well described and illustrated that they would seem to convince everybody, who tries to figure out the movements of the foetus through the birth canal, of the logic in the author's explanation of the mechanism of labour.

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price $ 4.75.

ANNOTATIONS

THE PROGNOSIS IN ANOREXIA NERVOSA

Since the clinical picture of anorexia nervo was described in 1874 by Sir William Gul there has been some discussion as regards th prognosis which, on the whole, has been est mated far more favourably by clinicians than b psychiatrists. The probable reason for this is th the experiences originate from differently selecte materials.

J. C. Beck and K. Brøchner-Mortense have recently undertaken an investigation of th material from Medical Department A, The Un versity Hospital (Rigshospitalet), Copenhage The investigation concerns 28 females with typ cal, well-marked clinical pictures. The disea commenced at the age of 11—15 years in seve patients, 16—20 years in fifteen, 21—25 years i five and at 31 years in one patient.

On admission, the calculated weight defic varied between 14 and 34 kg. (31 lbs. — 75 lbs.). The majority were extremely emaciated. Th great majority of the patients presented defini mental abnormalities. In four patients, menstru tion was irregular and the remainder suffere from amenorrhoea. On examination of urinar gonadotropins in 16 patients, these were foun to be below the upper normal limit. In 17 pa tients, the urinary oestrogens were determine and found to be low in 14 and normal in 3. In patients, the urinary androgenic substances were determined (capon comb method) and found t be within the normal range for the age group. The excretion of neutral 17-ketosteroids was de creased in all cases examined.

On follow-up examination, 25 out of 28 patient were traced. Out of 17 patients with an observa tion period of 10—23 years, 2 suffered still fro more or less pronounced symptoms while 15 were completely well and led a normal life. Out of patients in whom the period of observation wa shorter, 2 were still ill, 1 had died following in creasing anorexia at home and 5 were well.

15 out of 24 patients, who were unmarried o admission, had become married and 13 had un dergone 1—3 pregnancies. One of the childre suffered from anorexia nervosa.

References:

Beck, J. C. & K. Brøchner-Mortensen: Acta Med. Scand. 1954, *145:* 409.